

VAN LEEUWENHOEK LECTURE ON BIOSCIENCE

FROM PETRI NETS TO PARTIAL DIFFERENTIAL EQUATIONS

- A PETRI NET PERSPECTIVE ON SYSTEMS AND SYNTHETIC BIOLOGY -

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BRANDENBURG TECHNICAL UNIVERSITY COTTBUS-SENFTENBERG
COMPUTER SCIENCE INSTITUTE

❑ FRAMEWORK

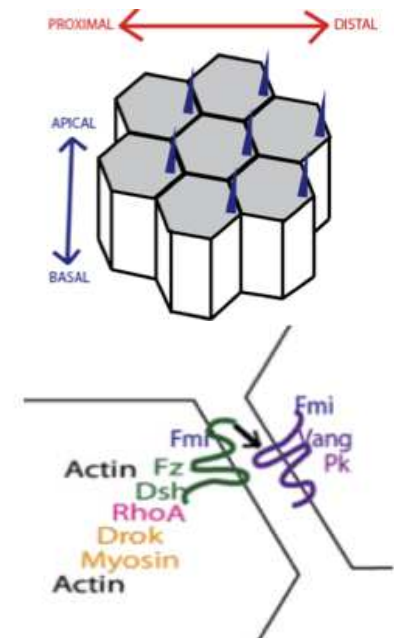
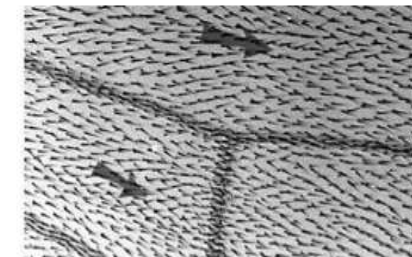
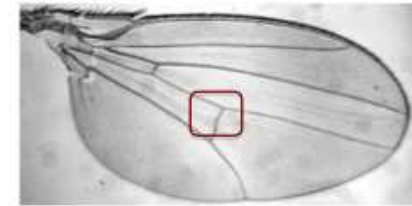
- > *unifying four paradigms:*
QPN - SPN - CPN - HPN
- > *our toolbox :*
Snoopy - Marcie - Charlie - Patty - S4

❑ MODELLING BIO PETRI NETS

- > *composition from standard components*
- > *bottom-up (reverse engineering)*
- > *genome-controlled model generation*

❑ COLOURED PETRI NETS

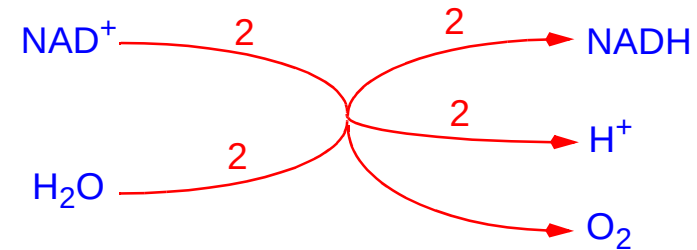
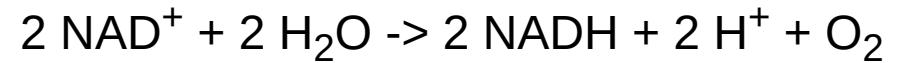
- > *colouring space -> PDE*
- > *Turing patterns*
- > *phase variation*
- > *planar cell polarity*



THE PETRI NET FRAMEWORK

...

**ARE NETWORKS
OF BIOCHEMICAL
REACTIONS**

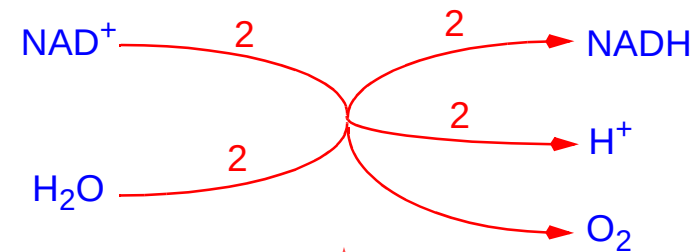
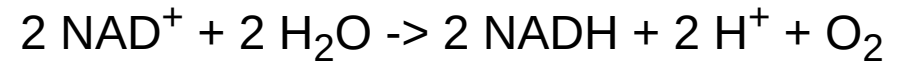


...

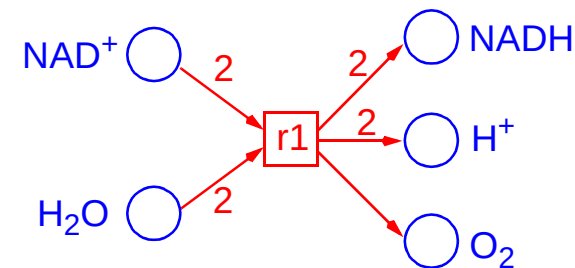
**ARE NETWORKS
OF BIOCHEMICAL
REACTIONS**

...

**NATURALLY
EXPRESSIBLE AS
PETRI NETS**



hyper-arcs



□ places -> model variables

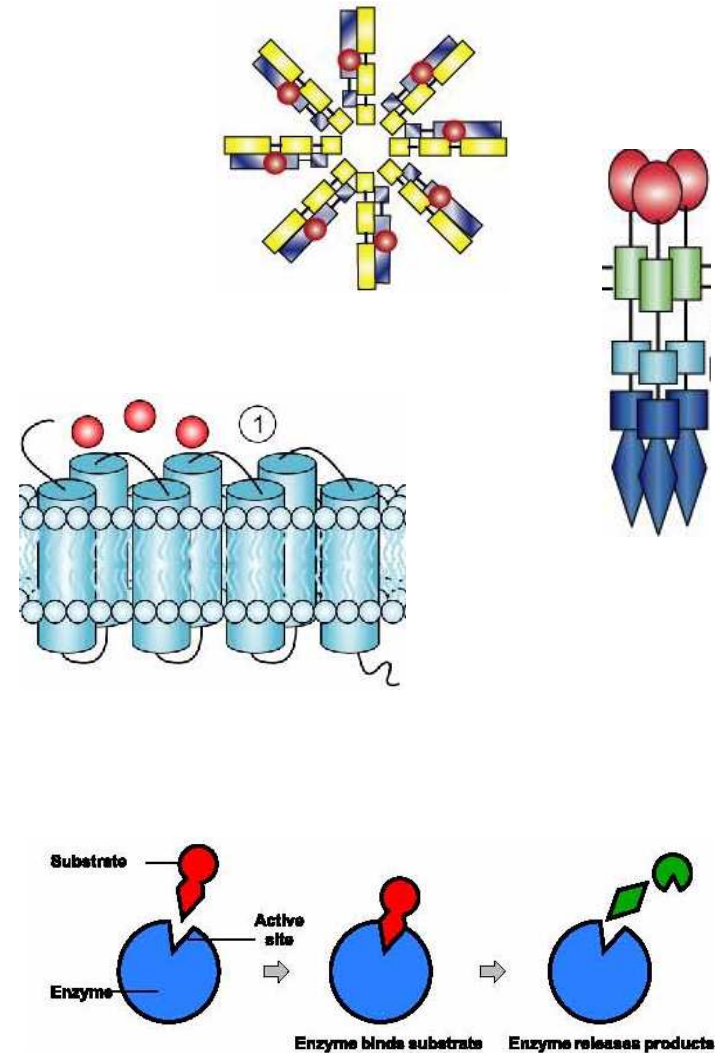
- > (bio-) chemical compounds
- > proteins
- > protein conformations
- > complexes
- > genes, . . . , etc.

. . . in different locations

□ transitions -> atomic events

- > (stoichiometric) chemical reaction
- > complexation / decomplexation
- > phosphorylation / dephosphorylation
- > conformational change
- > transport step, . . . , etc.

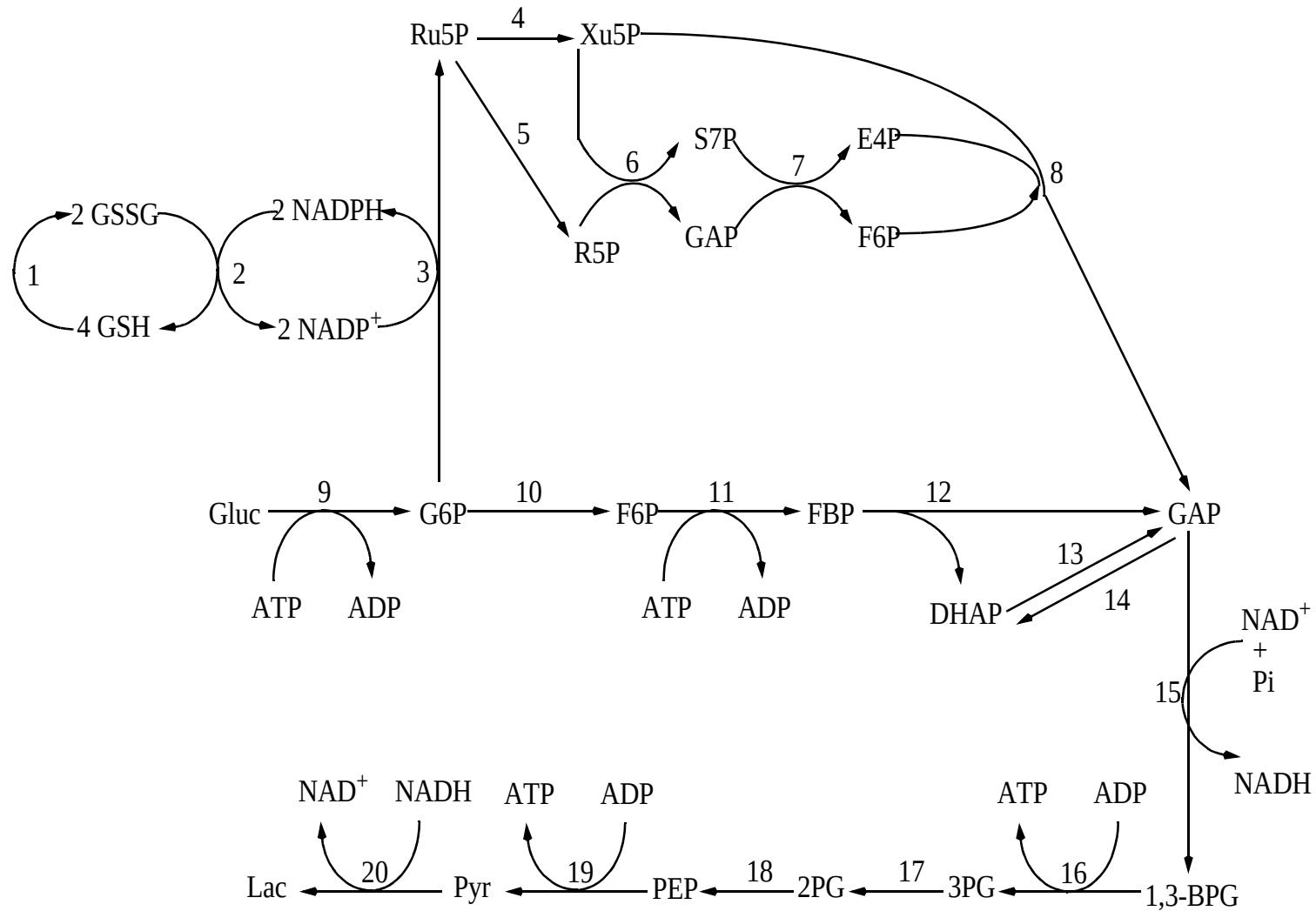
. . . in different locations



Ex1 - Glycolysis and Pentose Phosphate Pathway

PN & BioModel Engineering

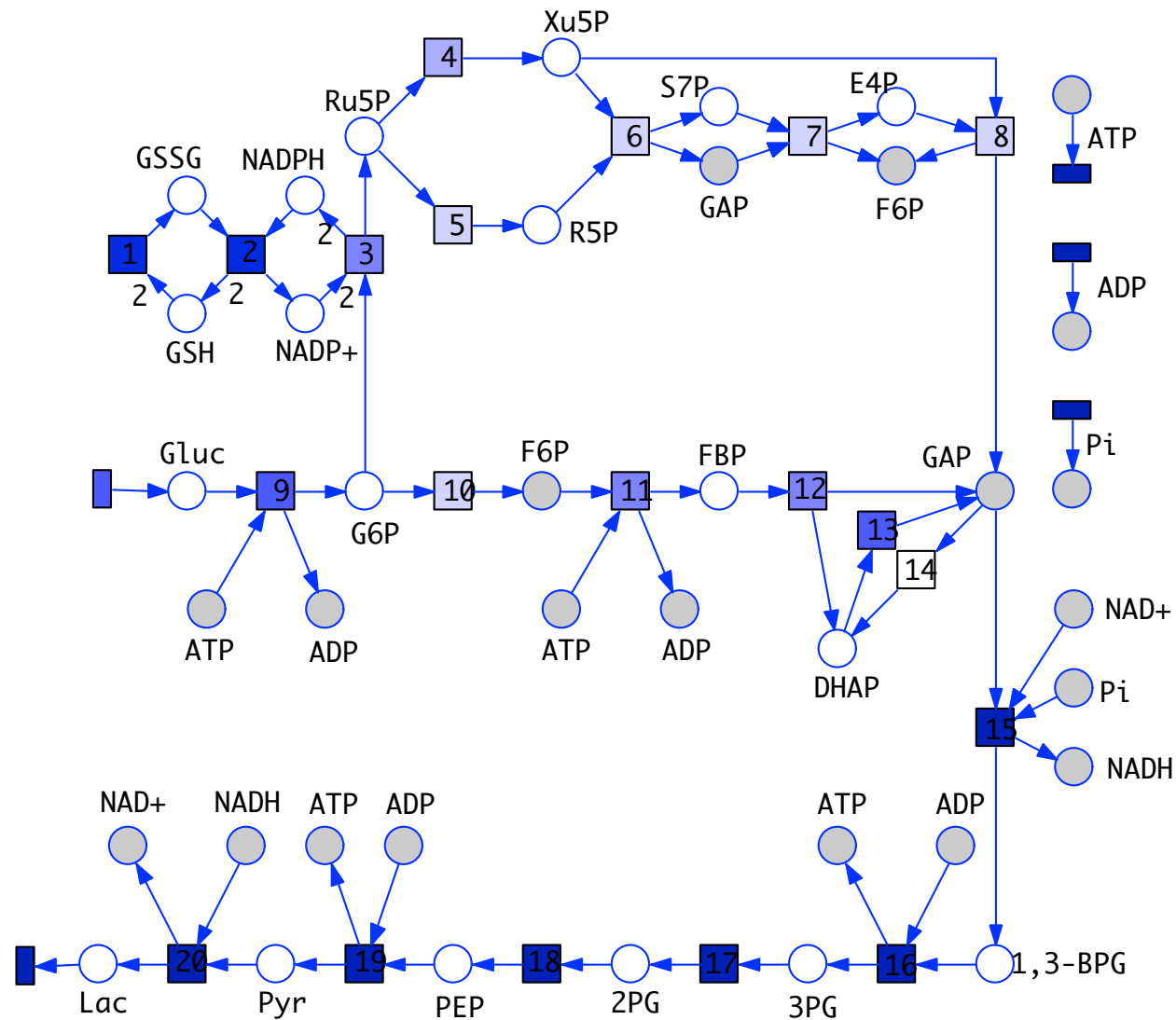
[Reddy 1993]



Ex1 - Glycolysis and Pentose Phosphate Pathway

PN & BioModel Engineering

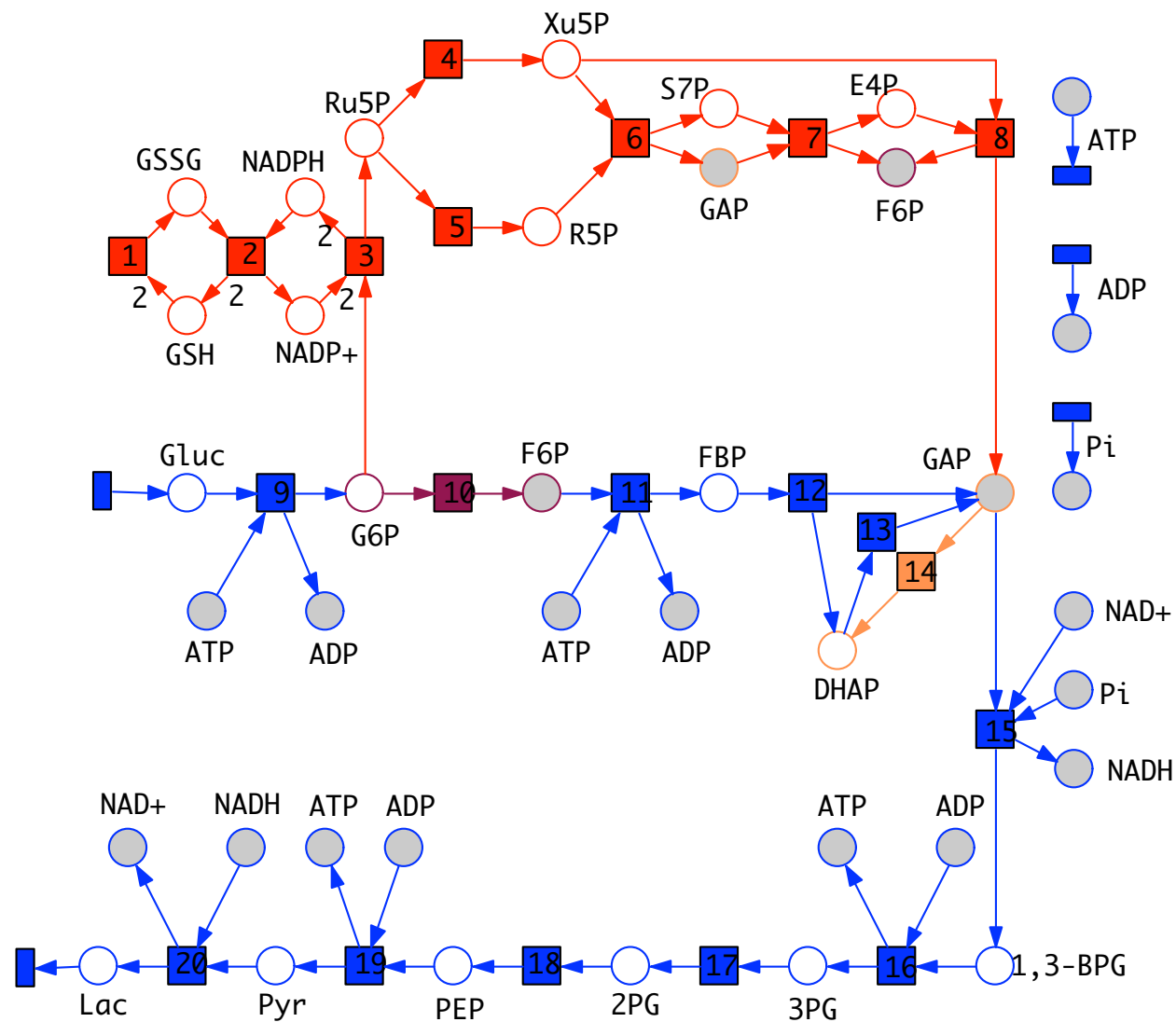
[Reddy 1993]
[Heiner 1998]



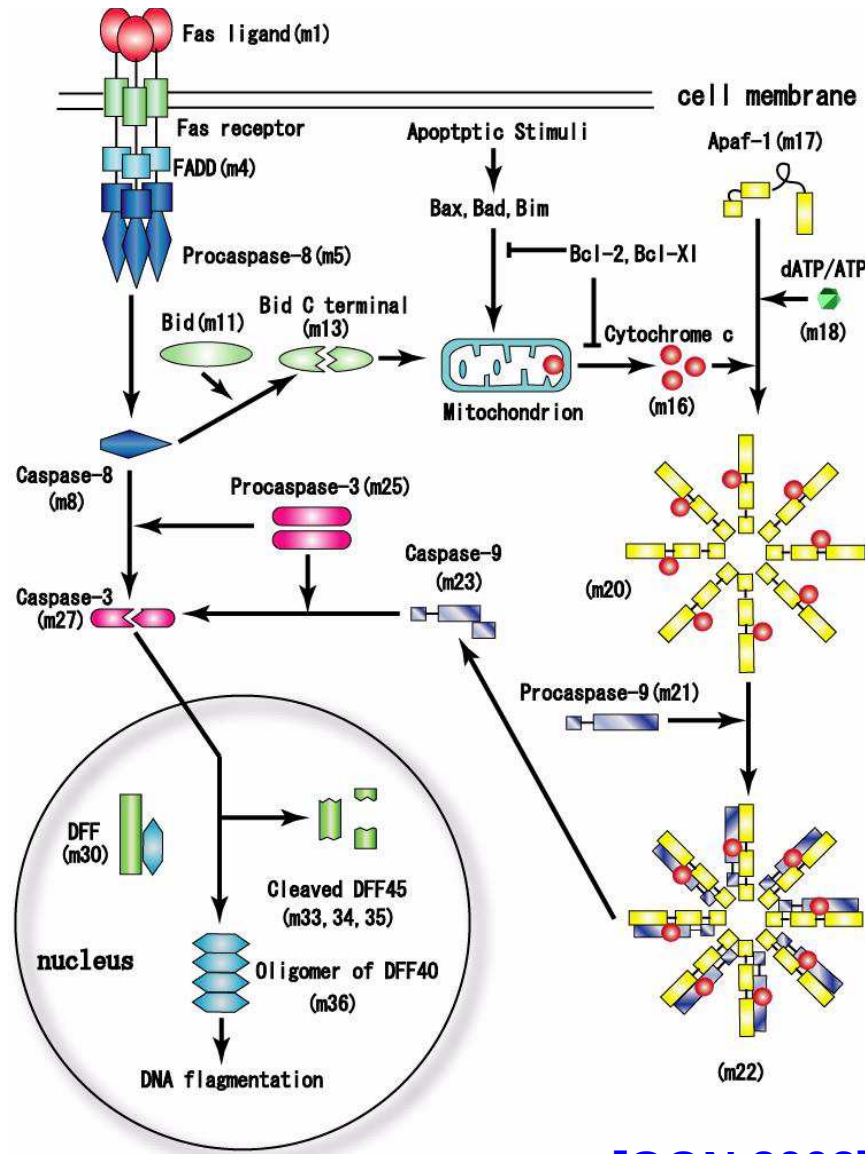
Ex1 - Glycolysis and Pentose Phosphate Pathway

PN & BioModel Engineering

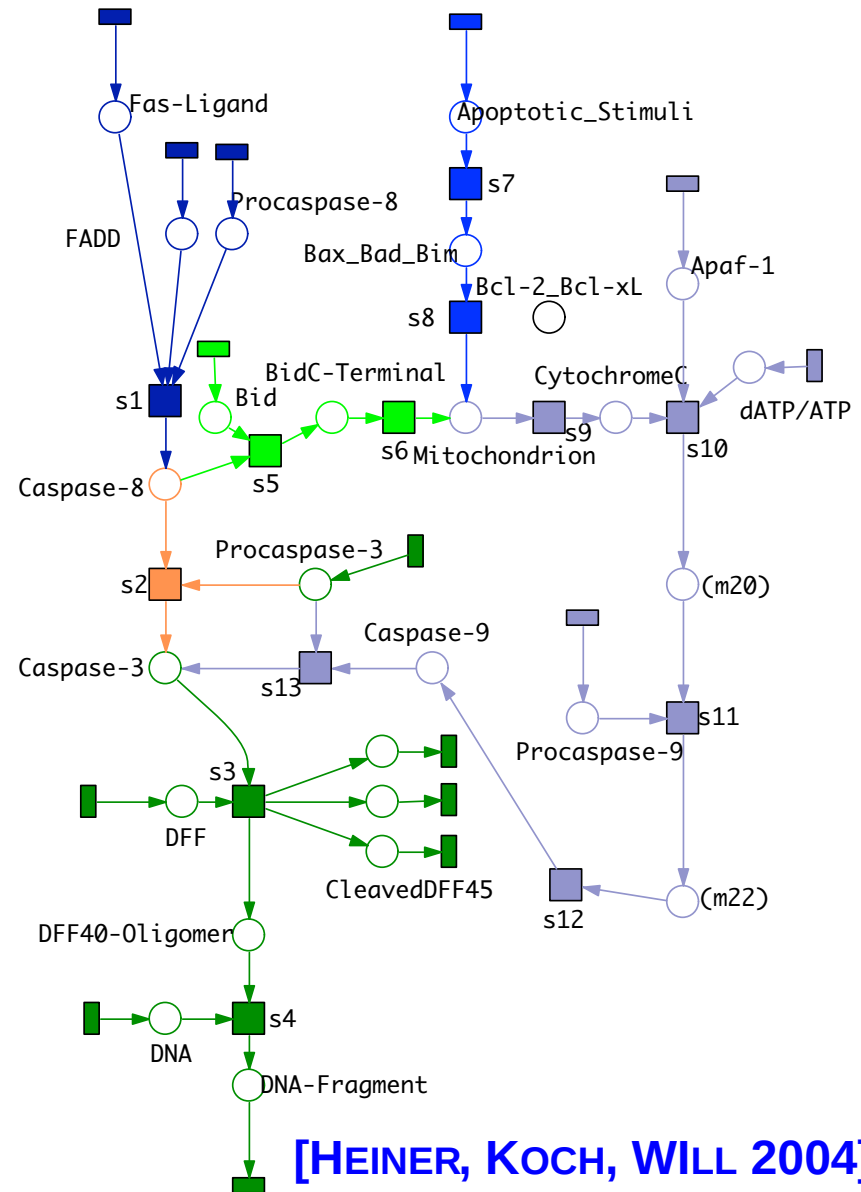
[Reddy 1993]
[Heiner 1998]



Ex2 - APOPTOSIS IN MAMMALIAN CELLS

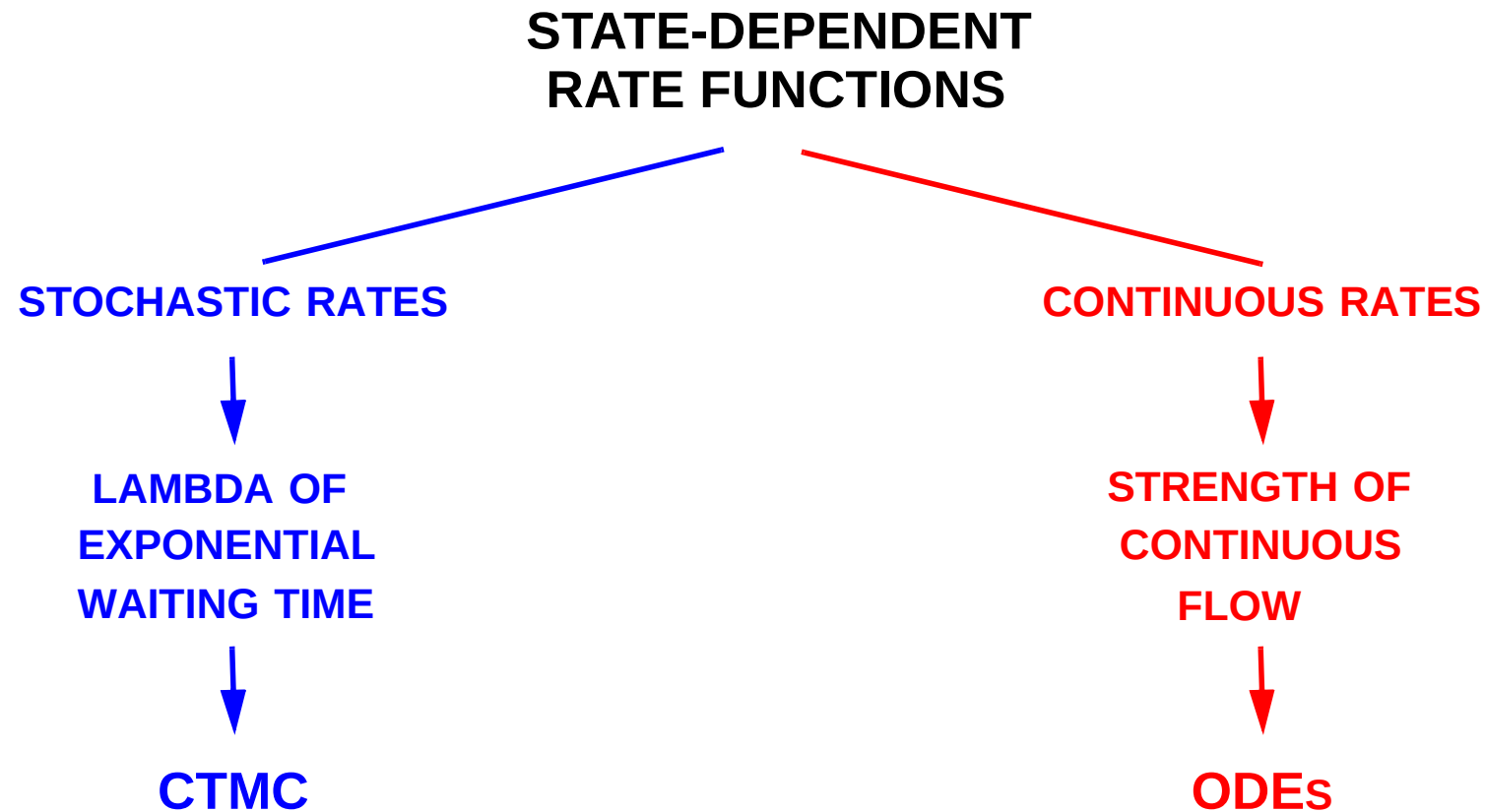


[GON 2003]



[HEINER, KOCH, WILL 2004]

STATE-DEPENDENT RATE FUNCTIONS

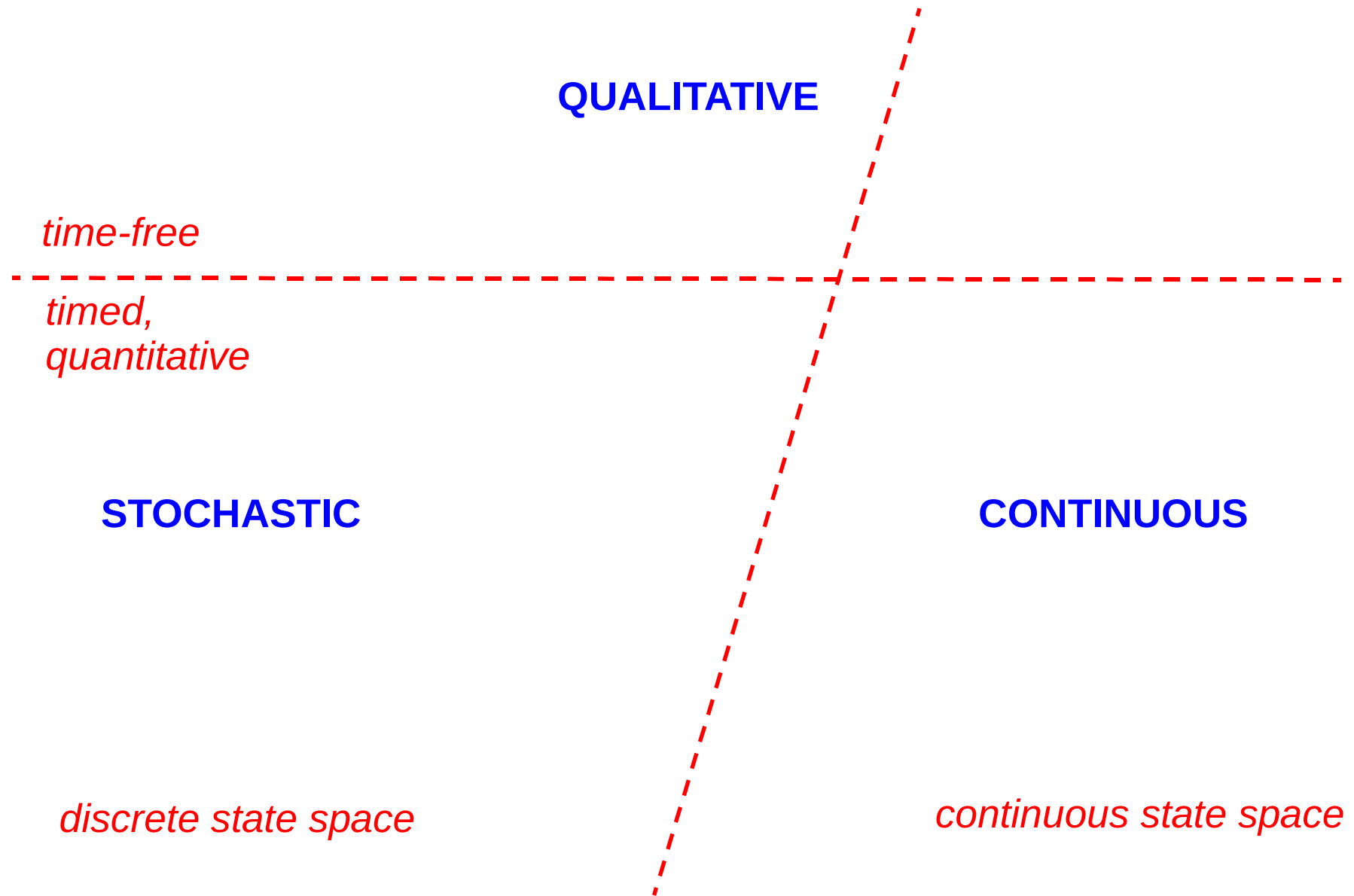


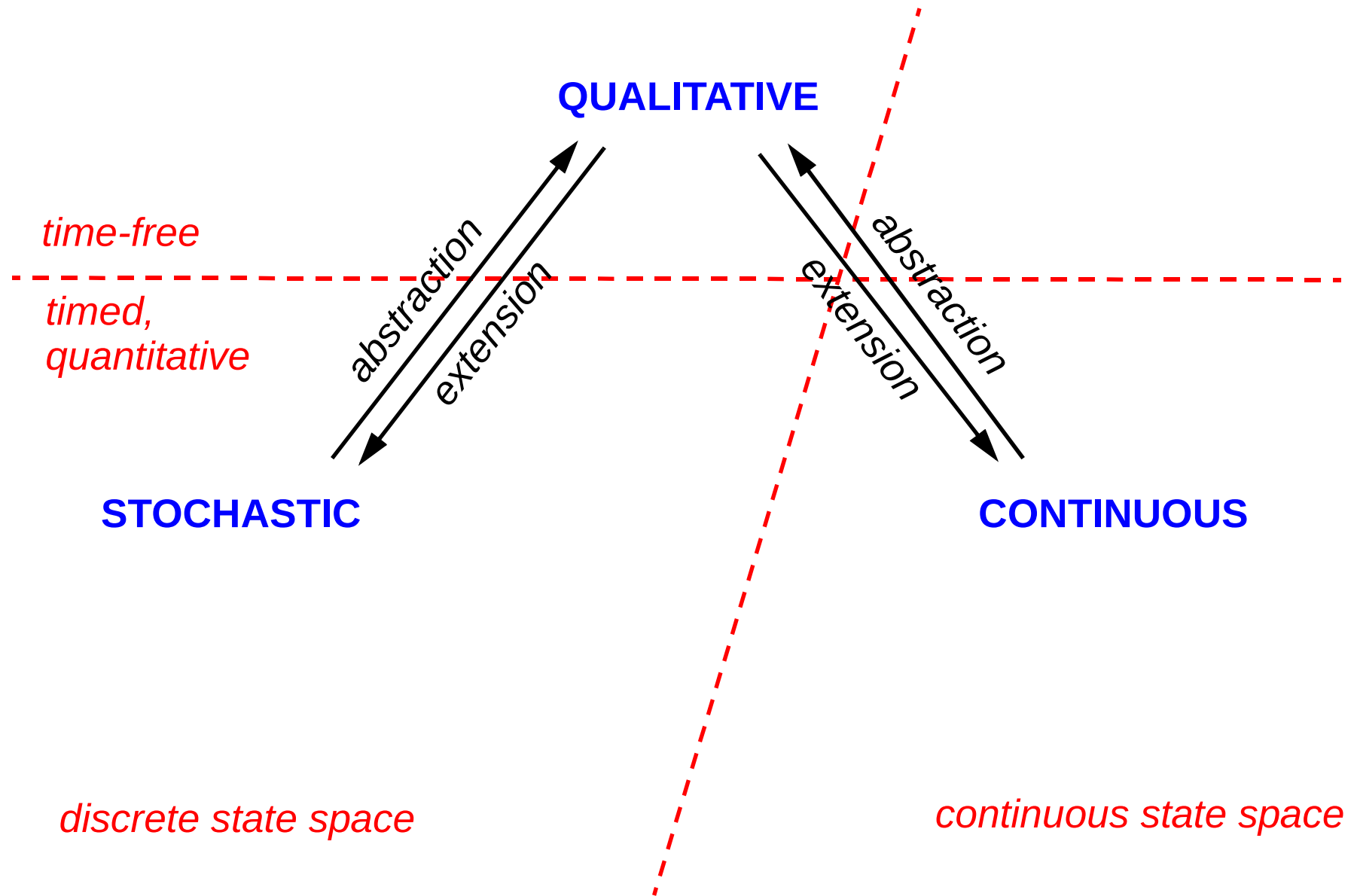
-> supported by, e.g., COPASI, Dizzy, ..., Snoopy

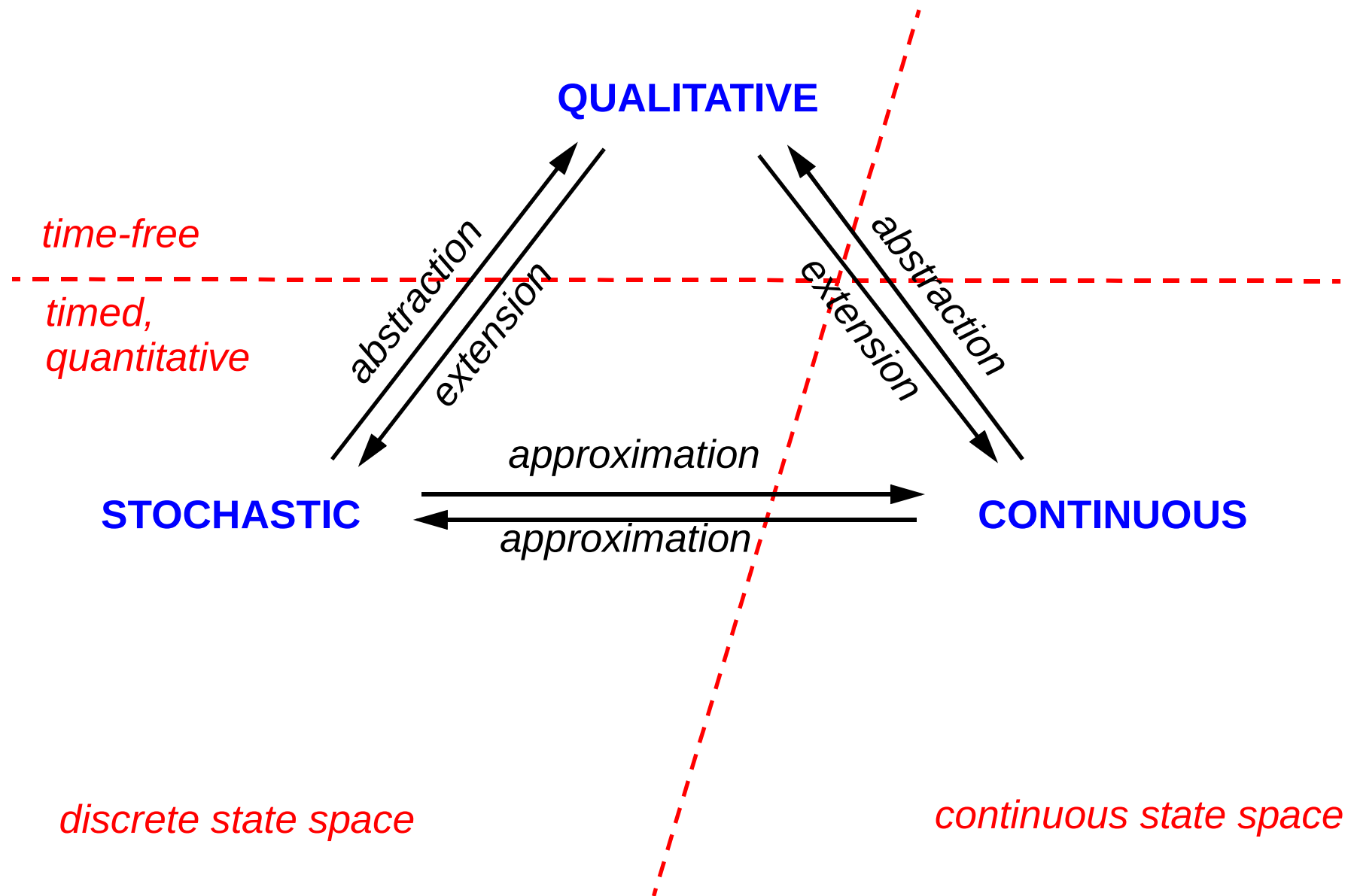
QUALITATIVE

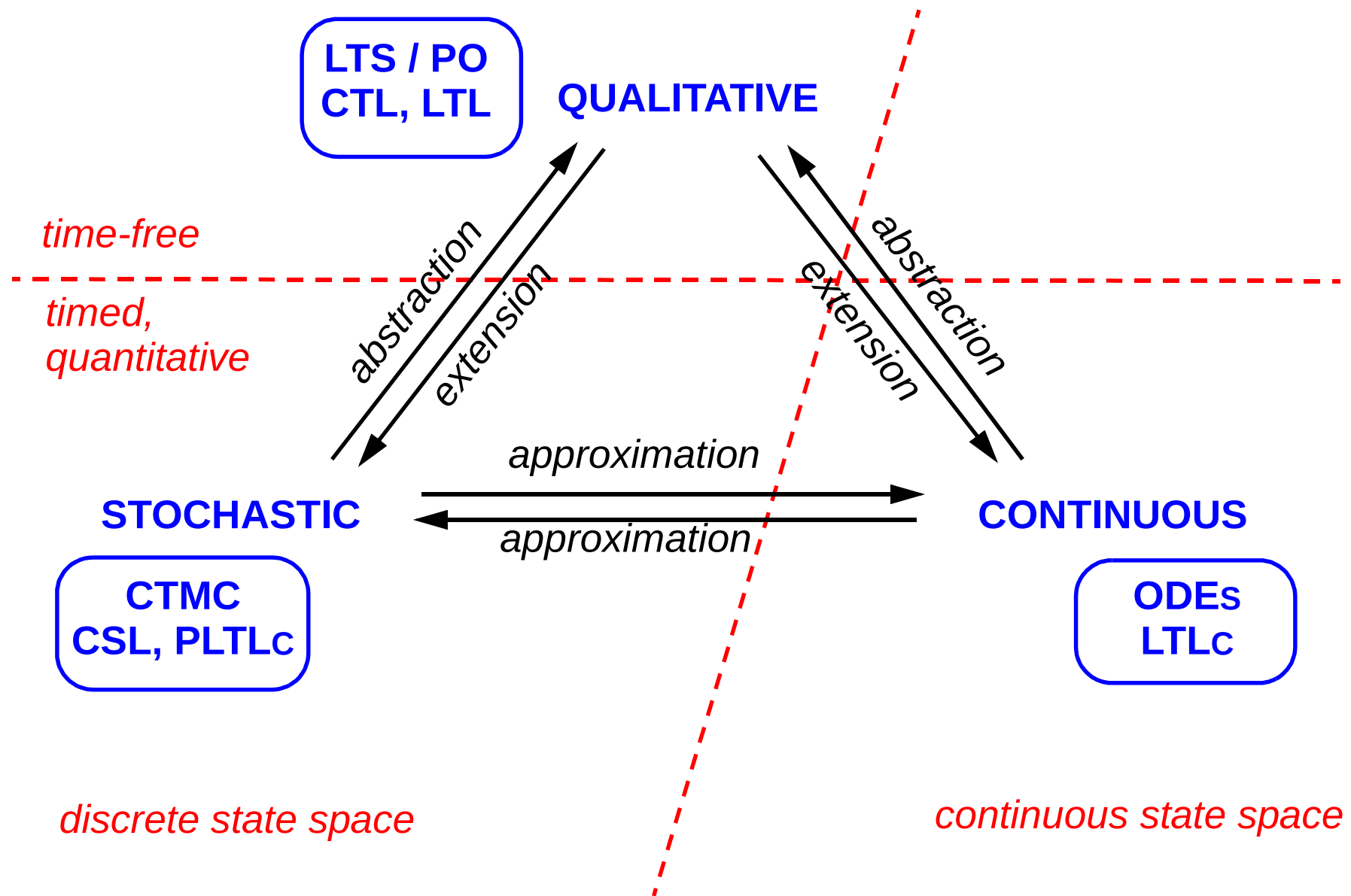
STOCHASTIC

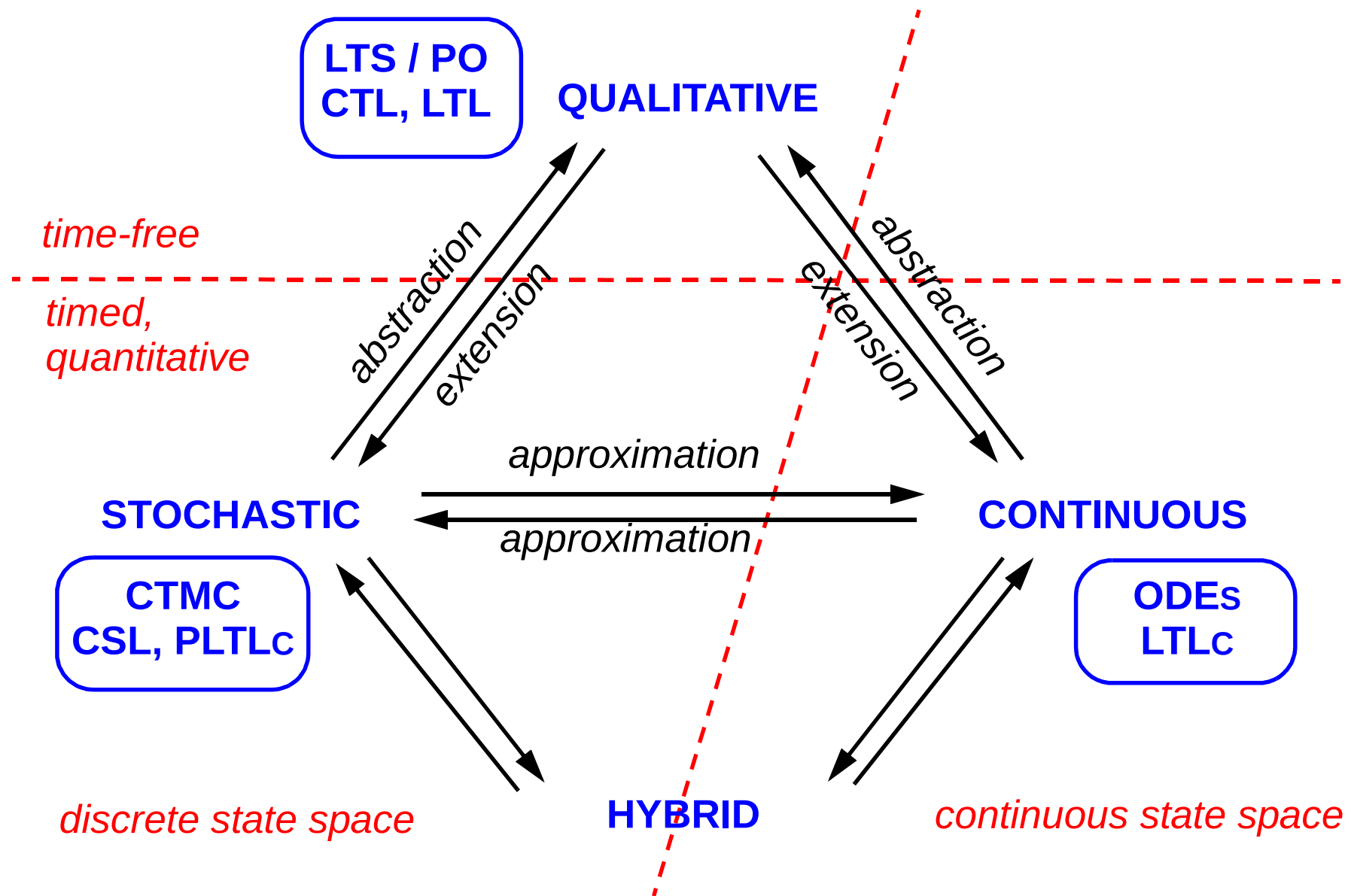
CONTINUOUS

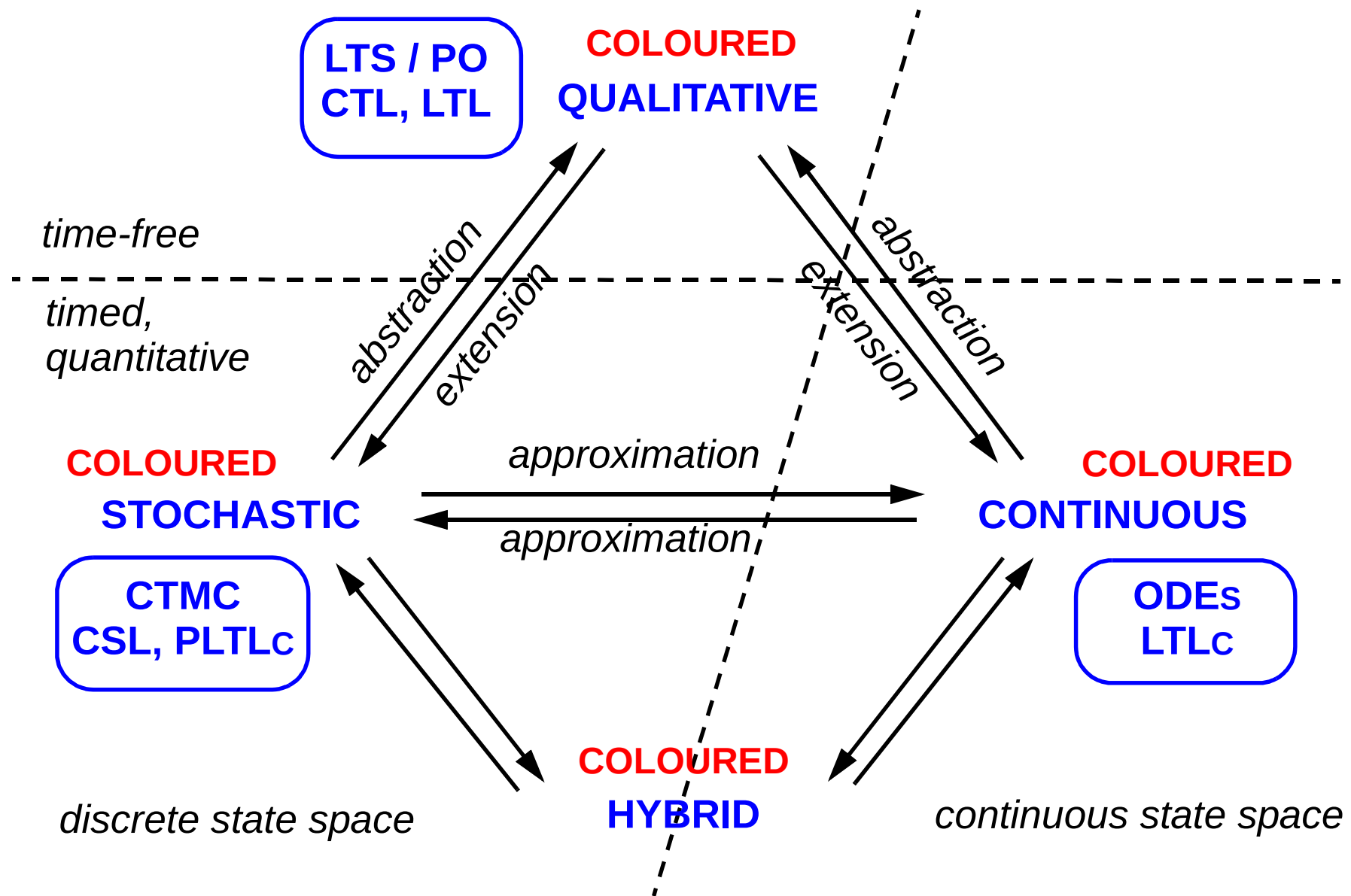






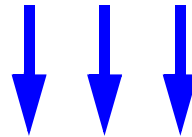




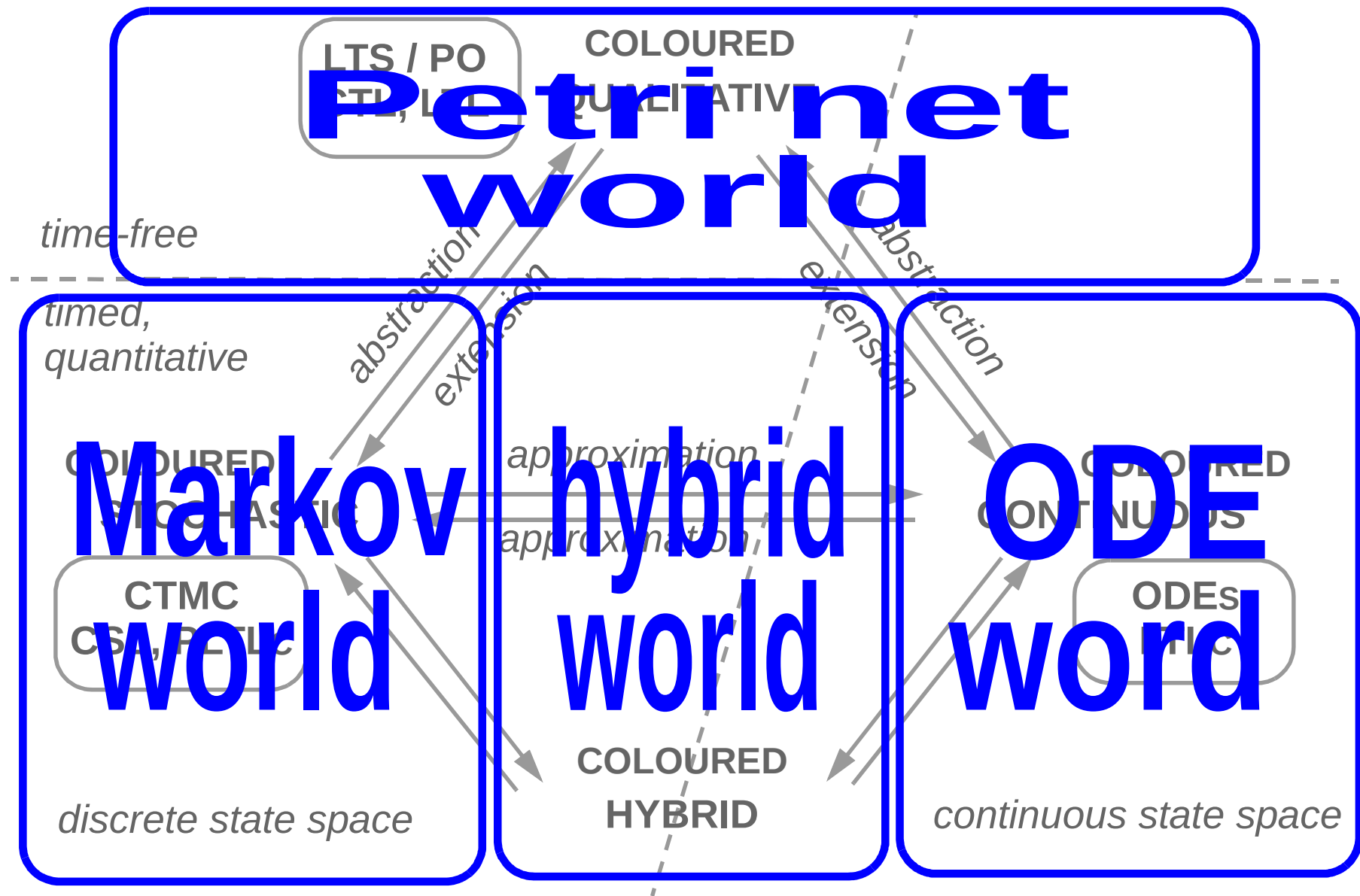


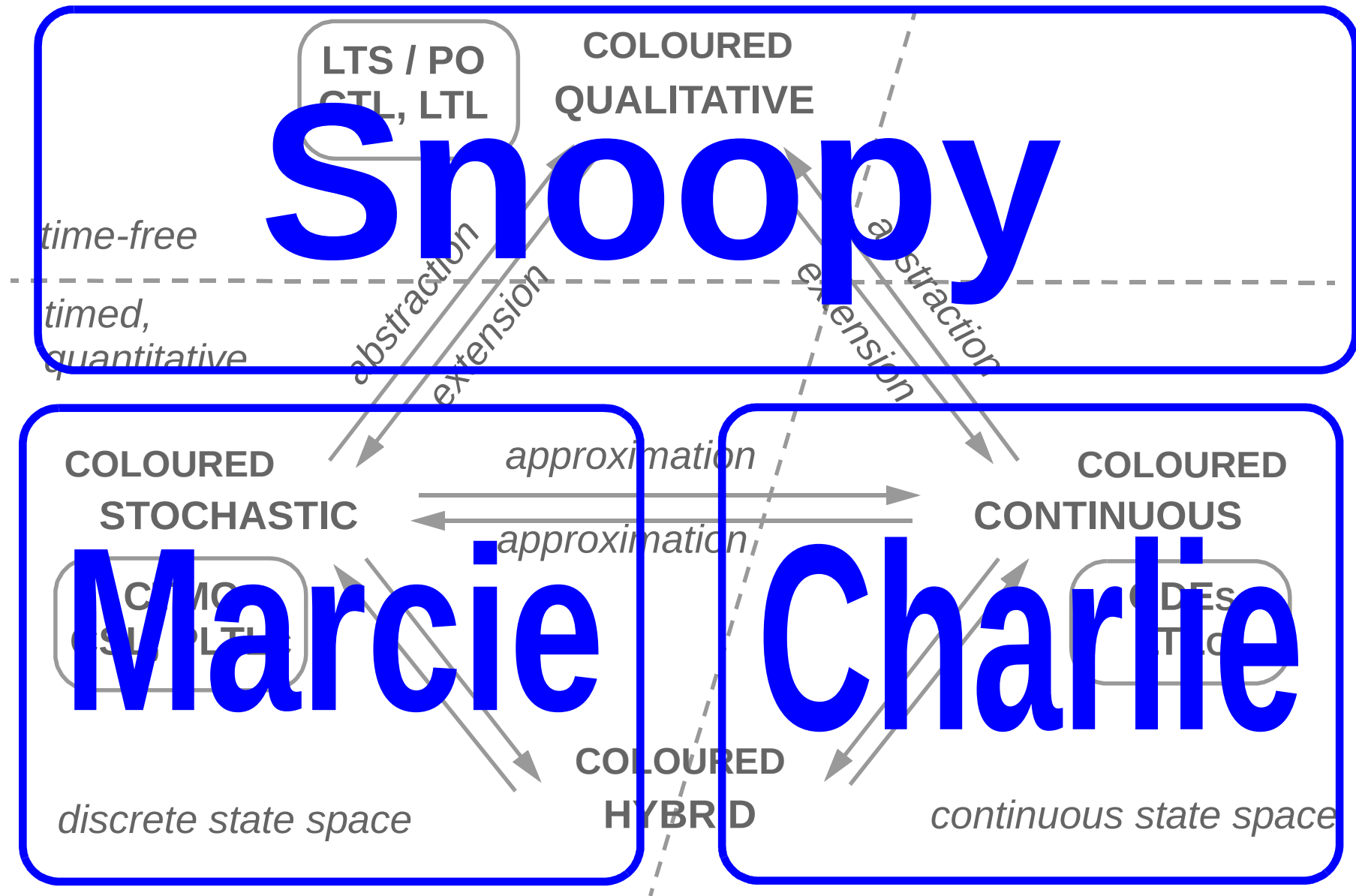
4x2

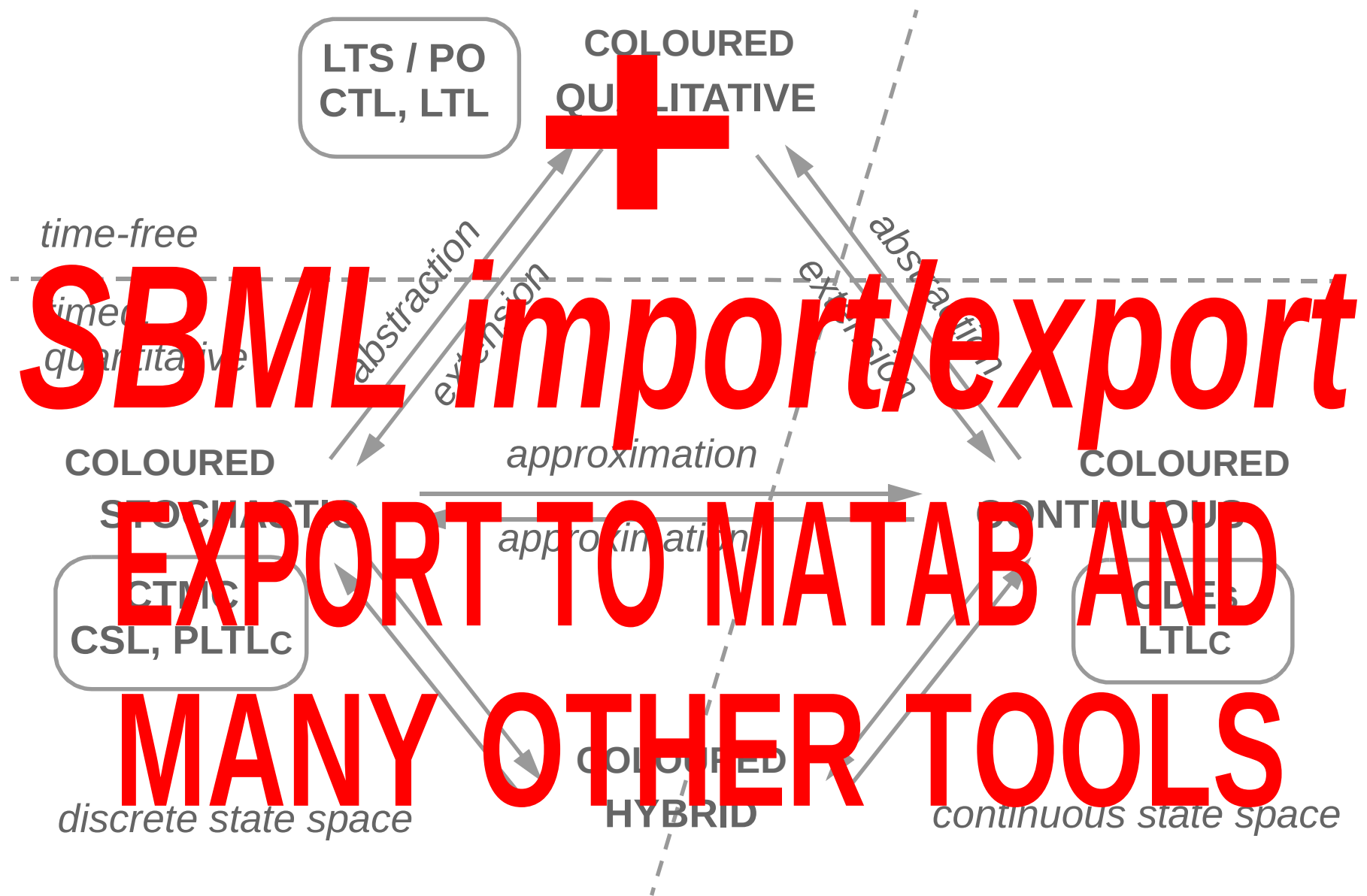
MODELS SHARING STRUCTURE



QUANTITATIVE MODEL = QUALITATIVE MODEL
+
RATE FUNCTIONS
(KINETICS)

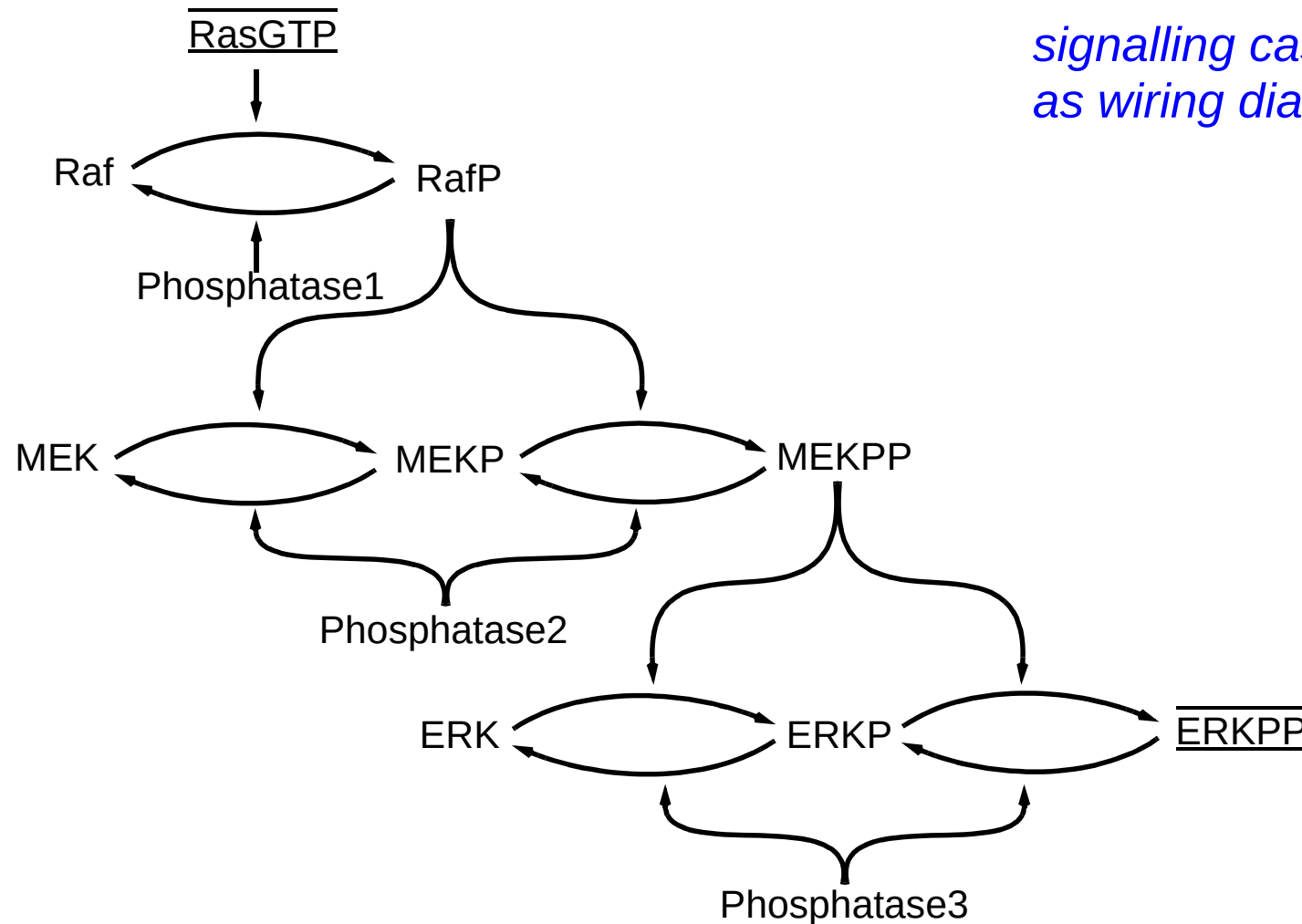






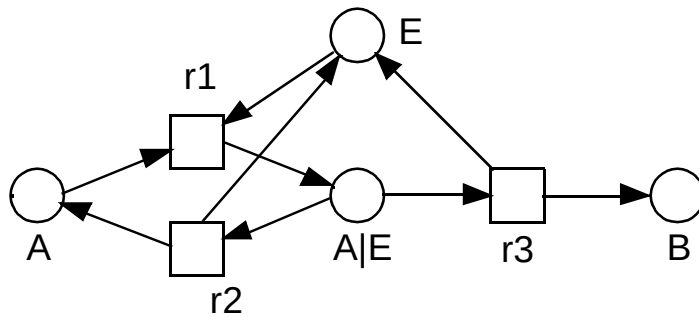
MODELLING Bio (PETRI) NETS

APPROACH 1



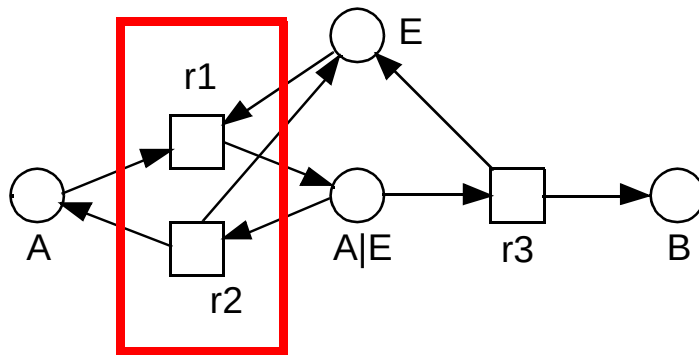


*enzymatic reaction,
mass-action kinetics*



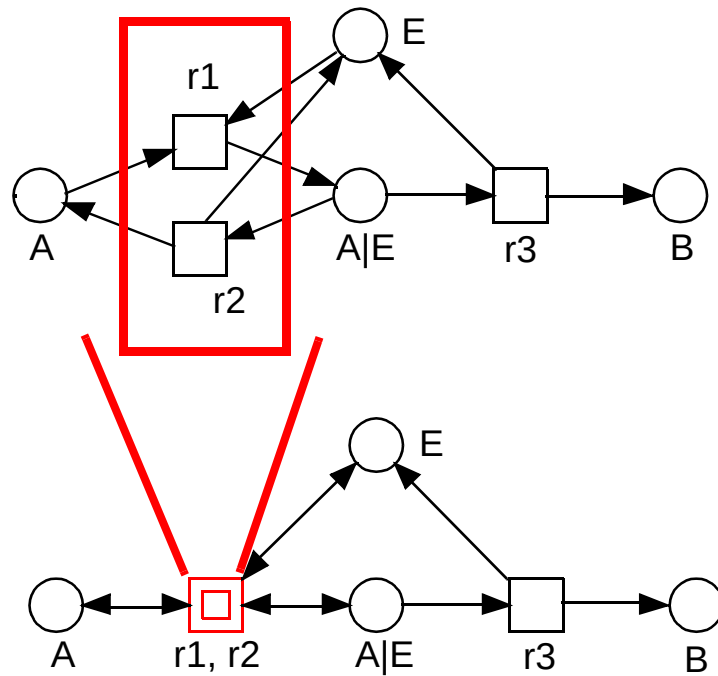


*enzymatic reaction,
mass-action kinetics*



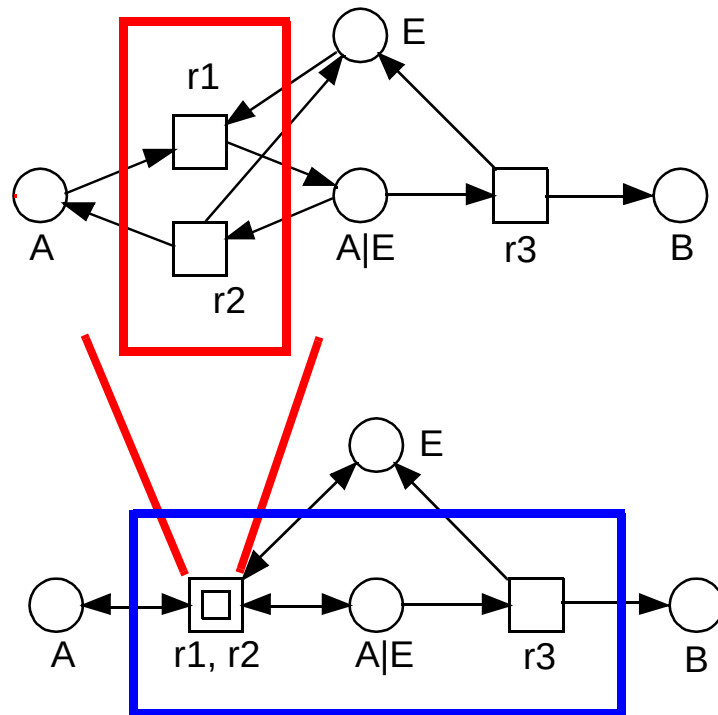


*enzymatic reaction,
mass-action kinetics*



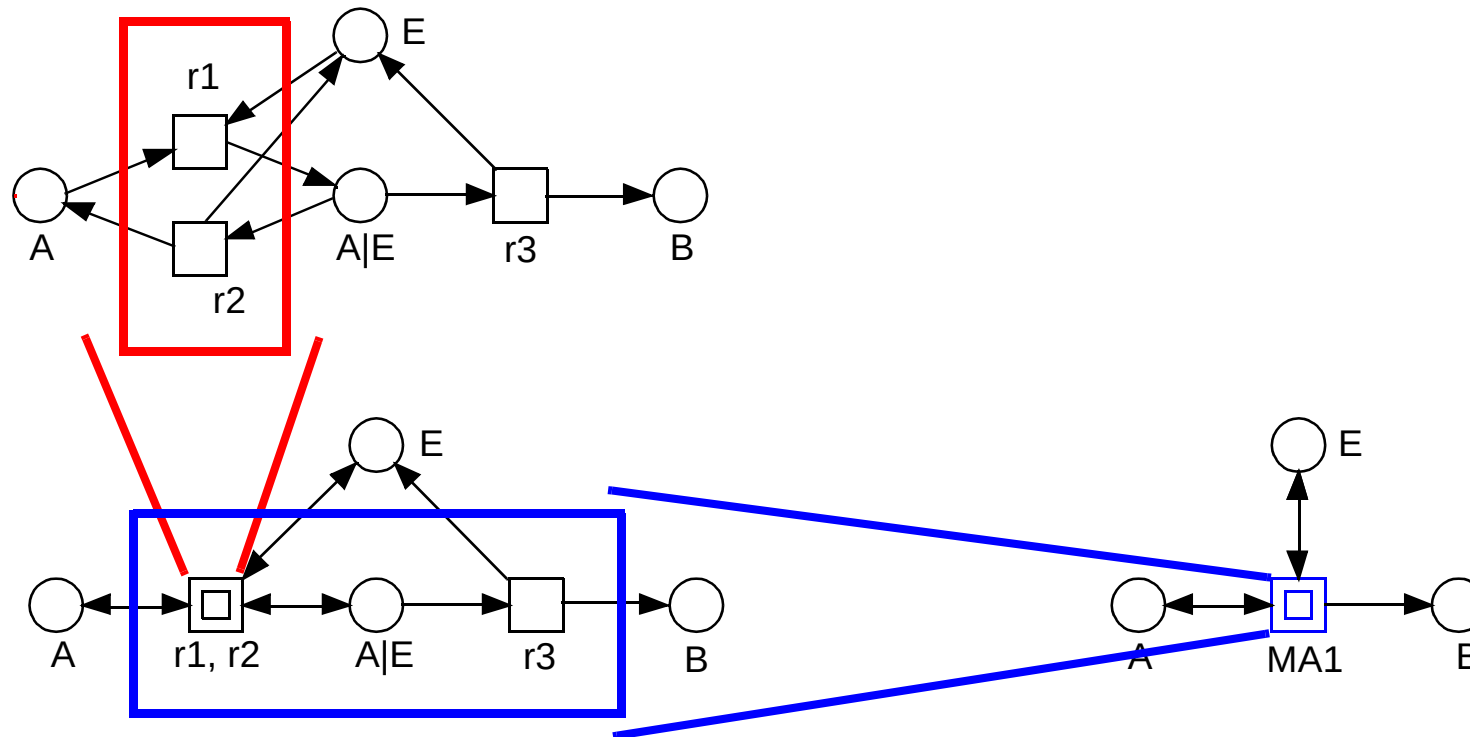


*enzymatic reaction,
mass-action kinetics*



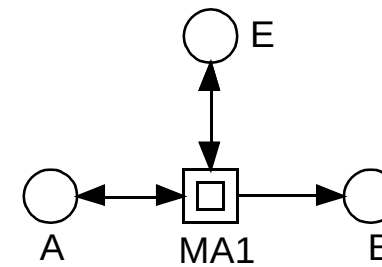
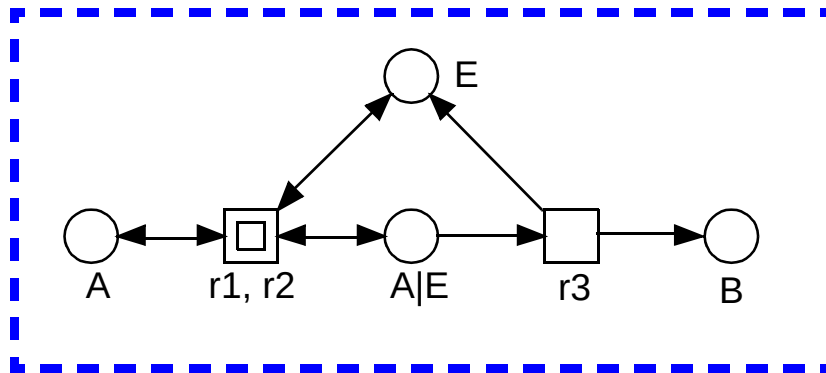
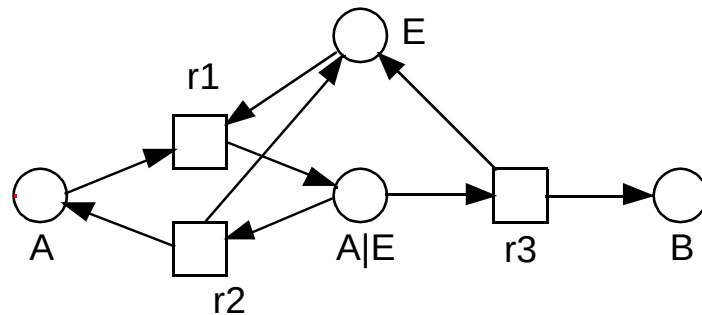


*enzymatic reaction,
mass-action kinetics*

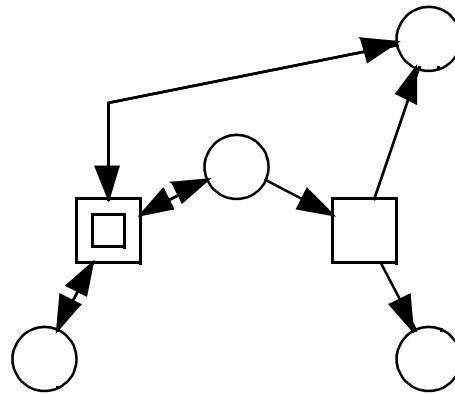


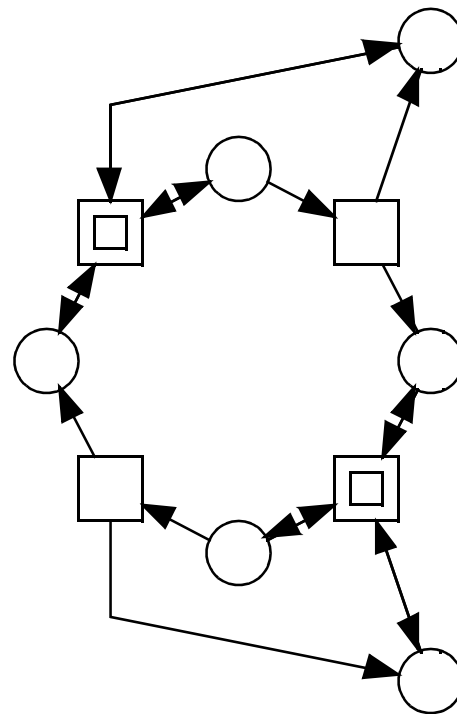


*enzymatic reaction,
mass-action kinetics*



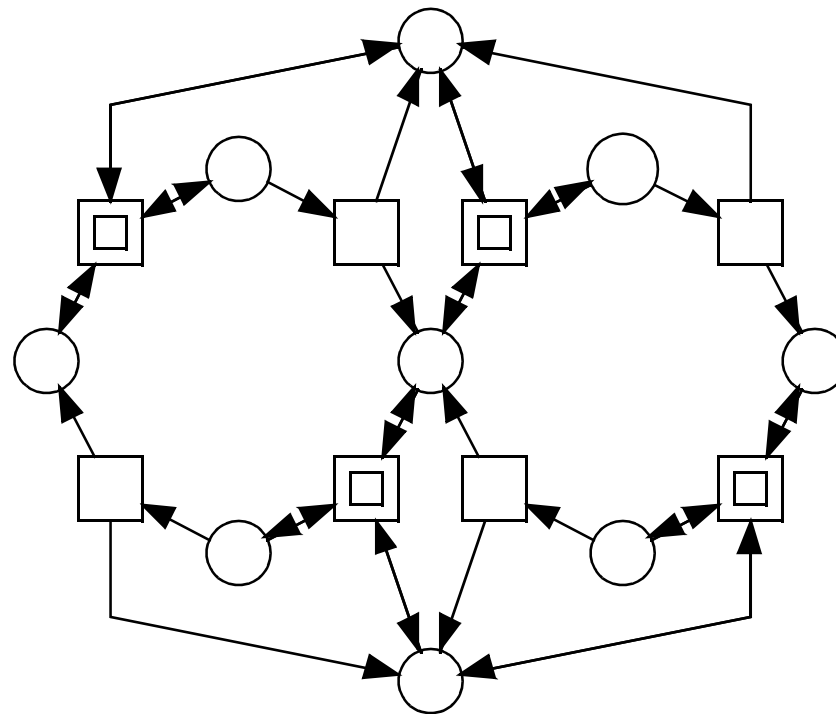
*SINGLE
MASS-ACTION STEP*

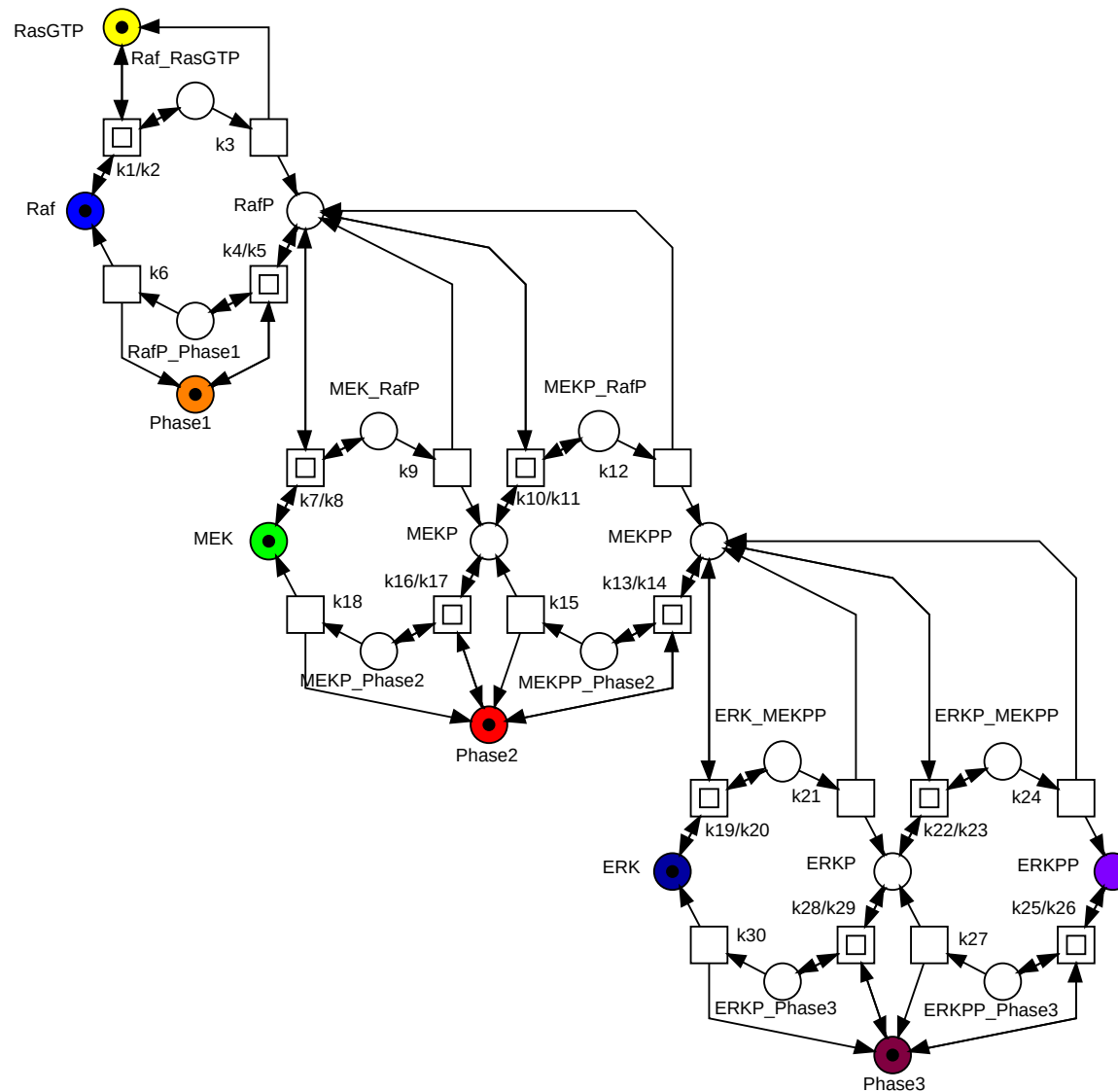




SINGLE
PHOSPHORYLATION / DEPHOSPHORYLATION

DOUBLE PHOSPHORYLATION / DEPHOSPHORYLATION

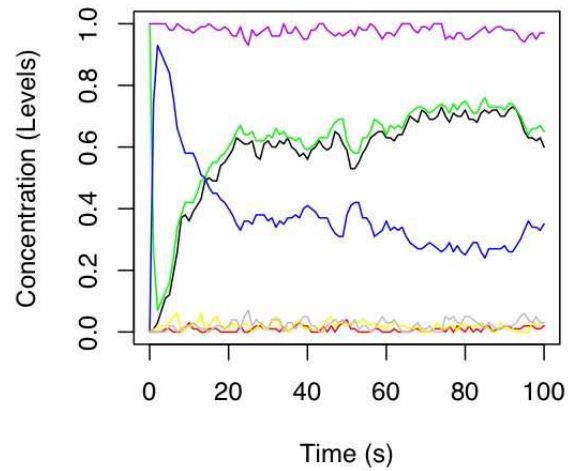




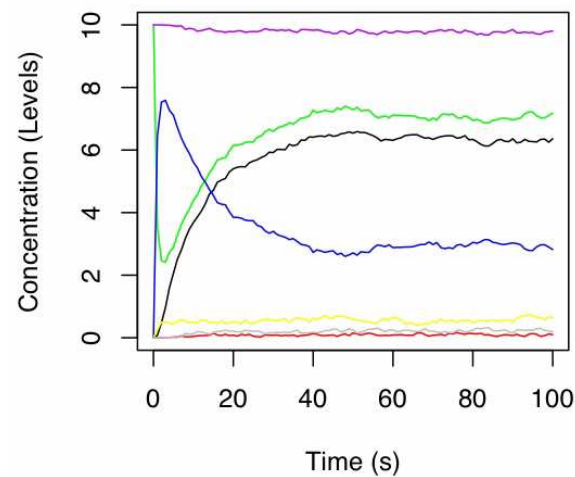
[GILBERT,
HEINER,
LEHRACK 2007]

[HEINER,
GILBERT,
DONALDSON 2008]

Stochastic Output – 1 Level



Stochastic Output – 10 Levels

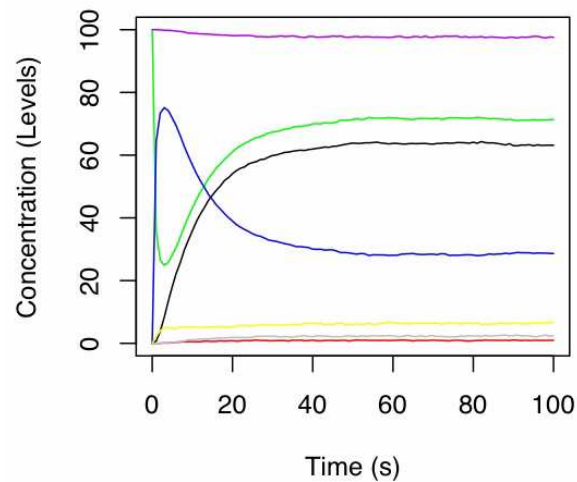


*signalling cascade
as wiring diagram*

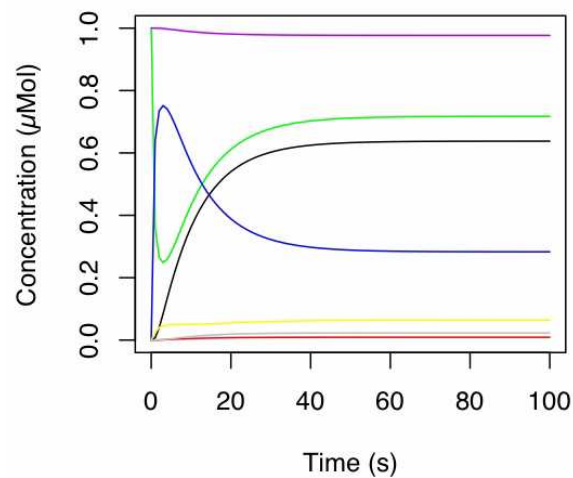
**[GILBERT,
HEINER,
LEHRACK 2007]**

**[HEINER,
GILBERT,
DONALDSON 2008]**

Stochastic Output – 100 Levels

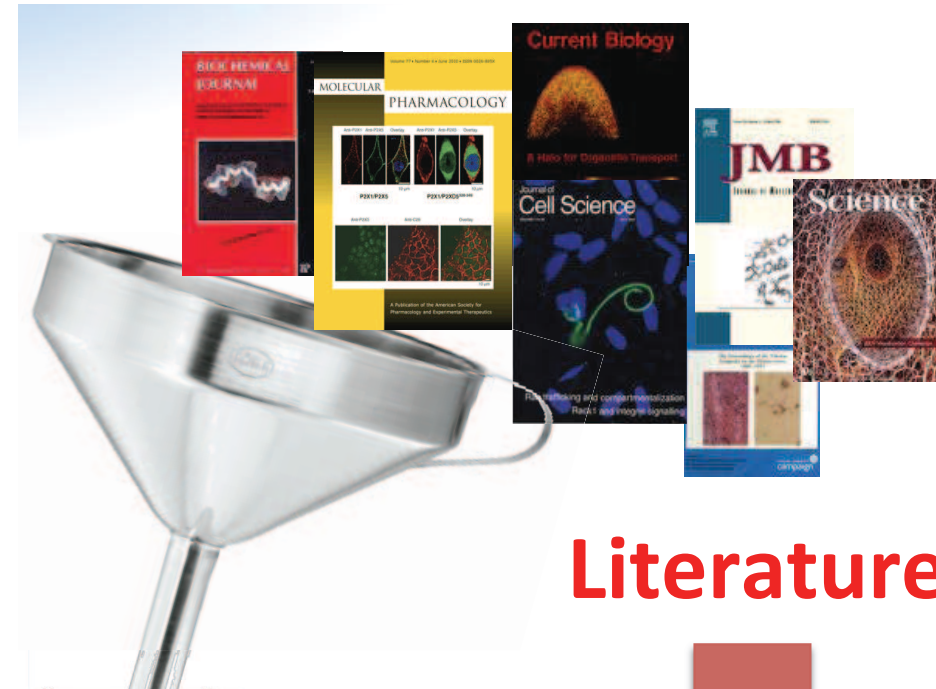
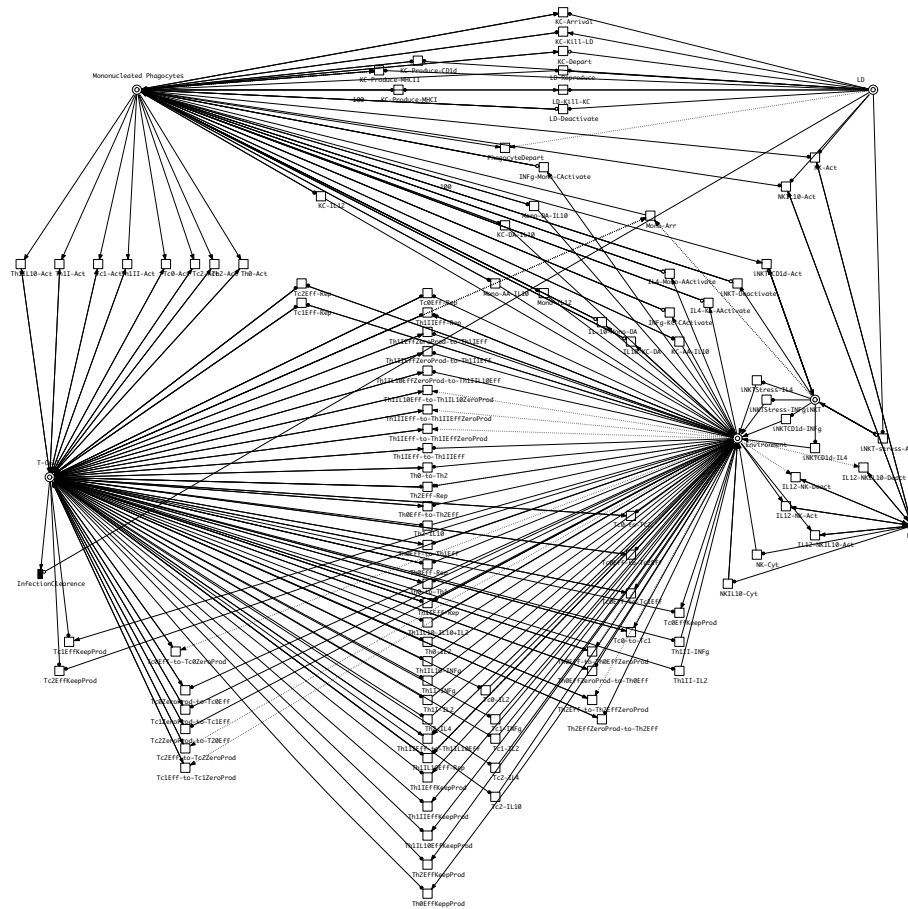


Deterministic Output

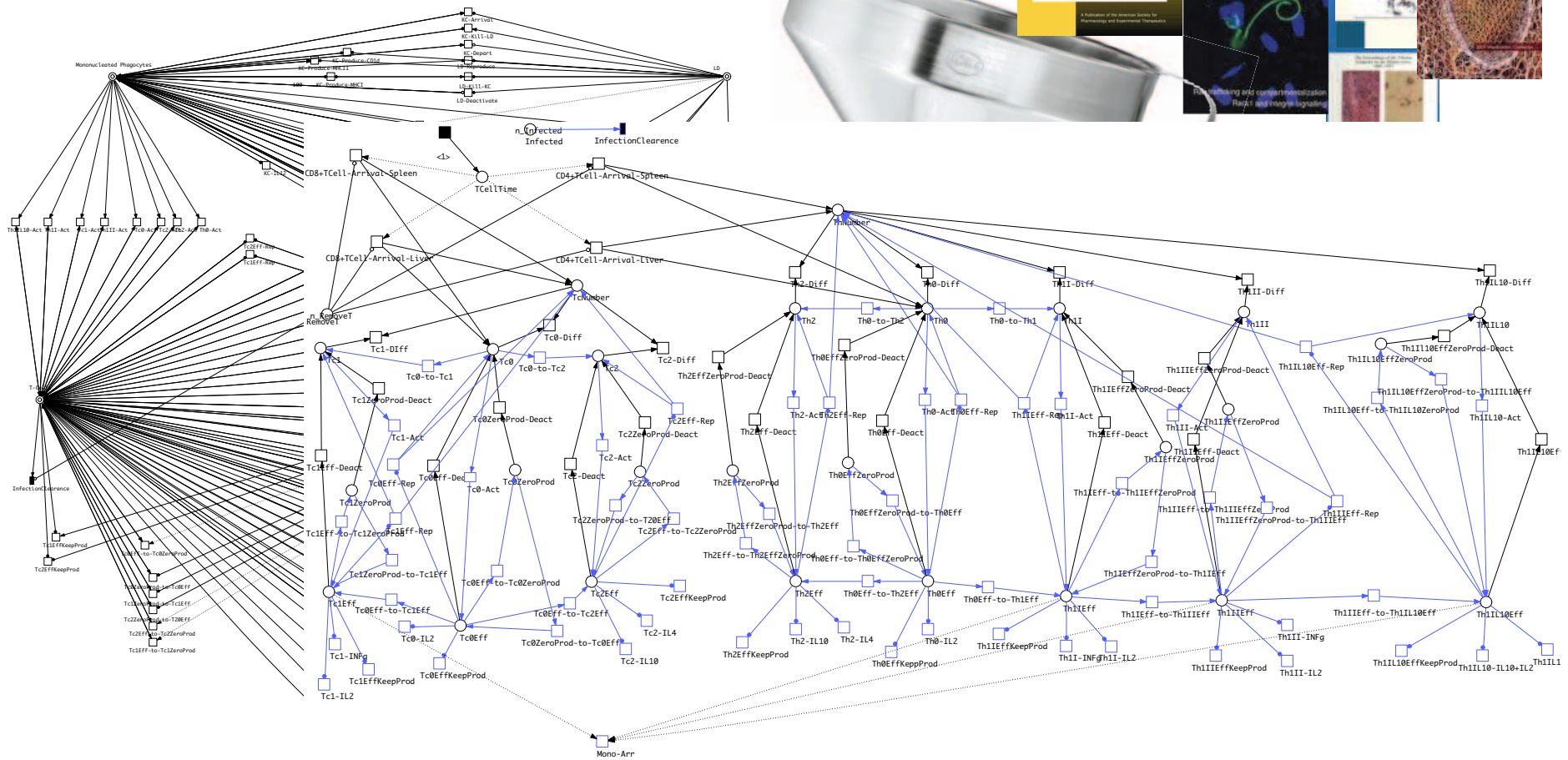


APPROACH 2

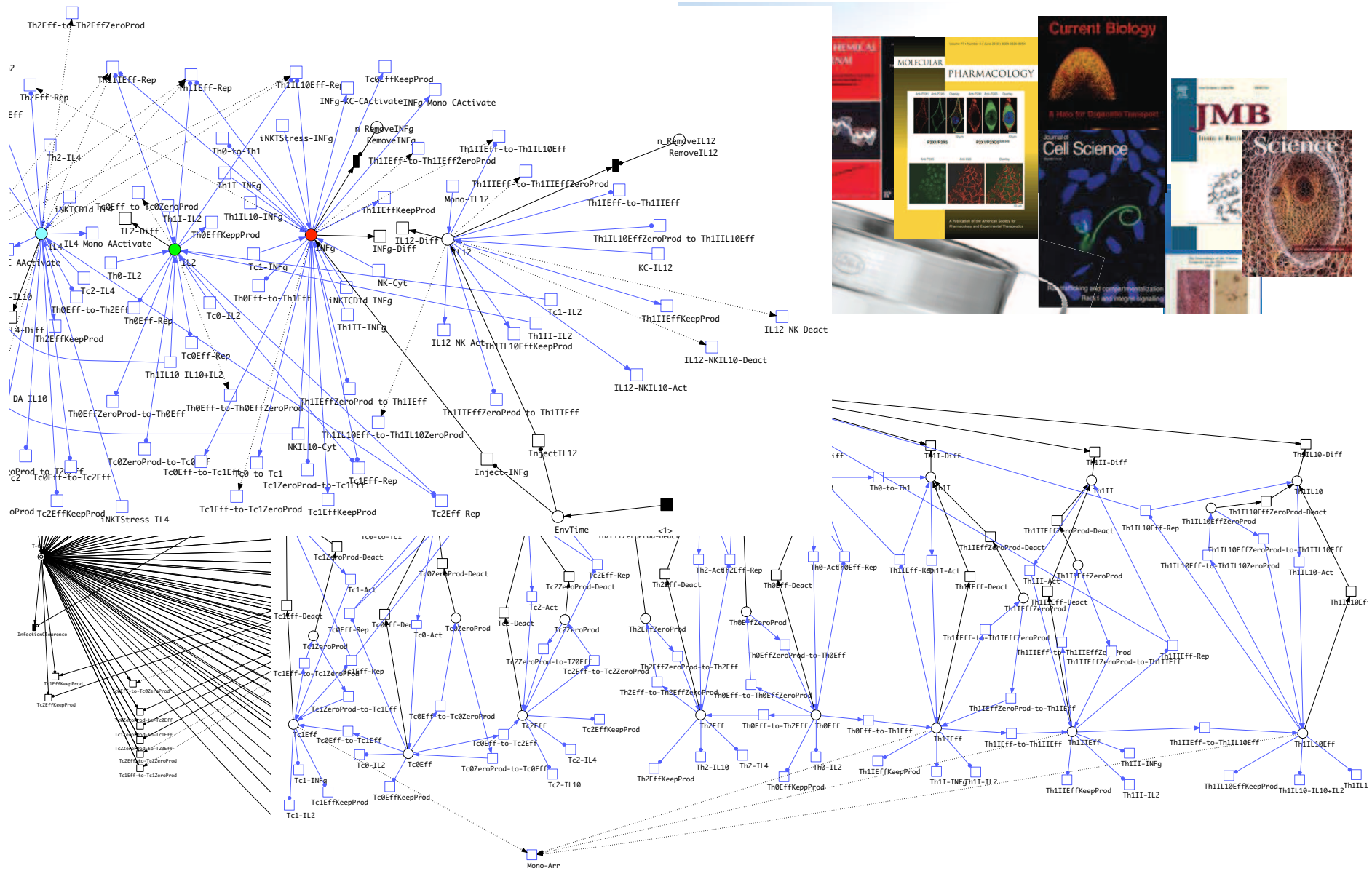




Literature

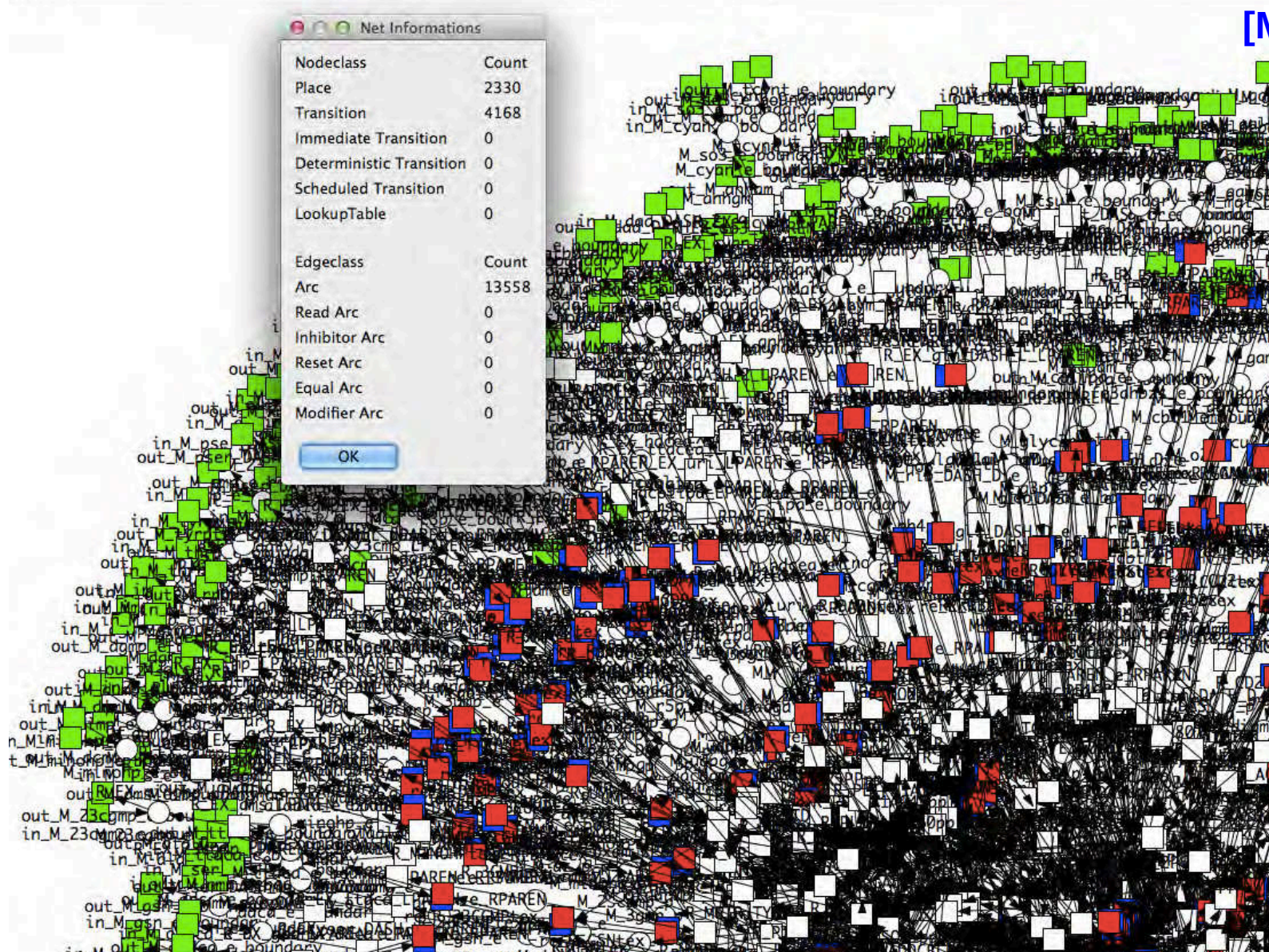


FROM LITERATURE TO MODELS



APPROACH 3

[Monk 2013]



HOW TO SURVIVE LARGER MODELS ?

HOW TO SURVIVE LARGER MODELS ?

-> MODULAR MODELLING

HOW TO SURVIVE LARGER MODELS ?

-> MODULAR MODELLING

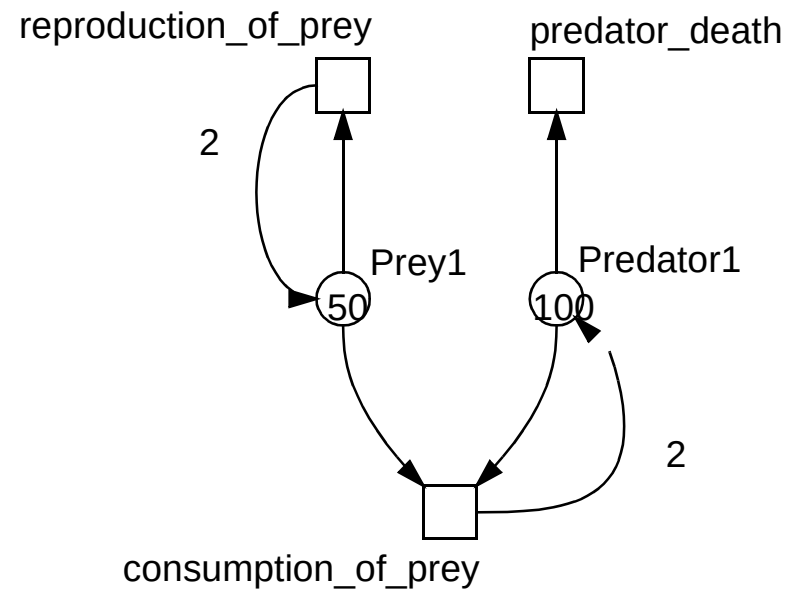
-> COLOURED PETRI NETS

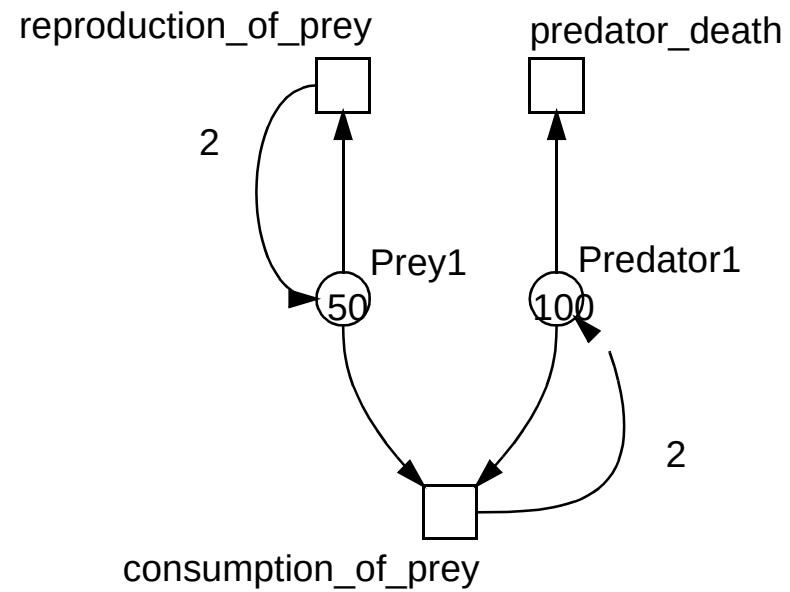
... AND THEN THERE WAS COLOUR

PN & BioModel Engineering

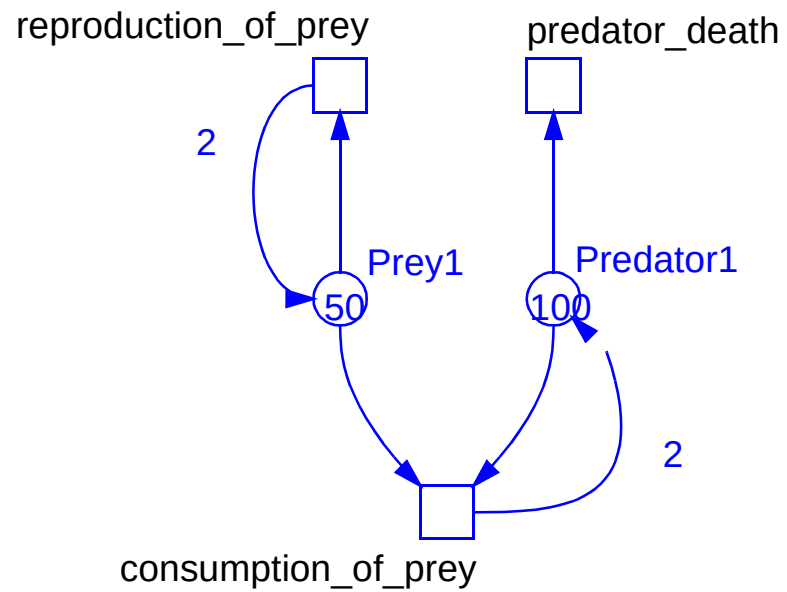


Kew Gardens, 24/04/2011

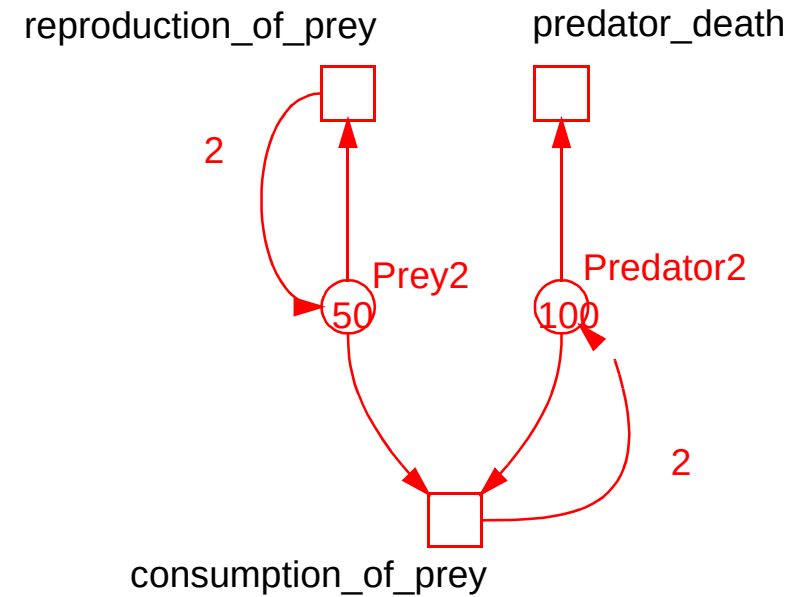




sub-system1



sub-system2



❑ definitions

colourset CS = 1-2;

var x : CS;

❑ better:

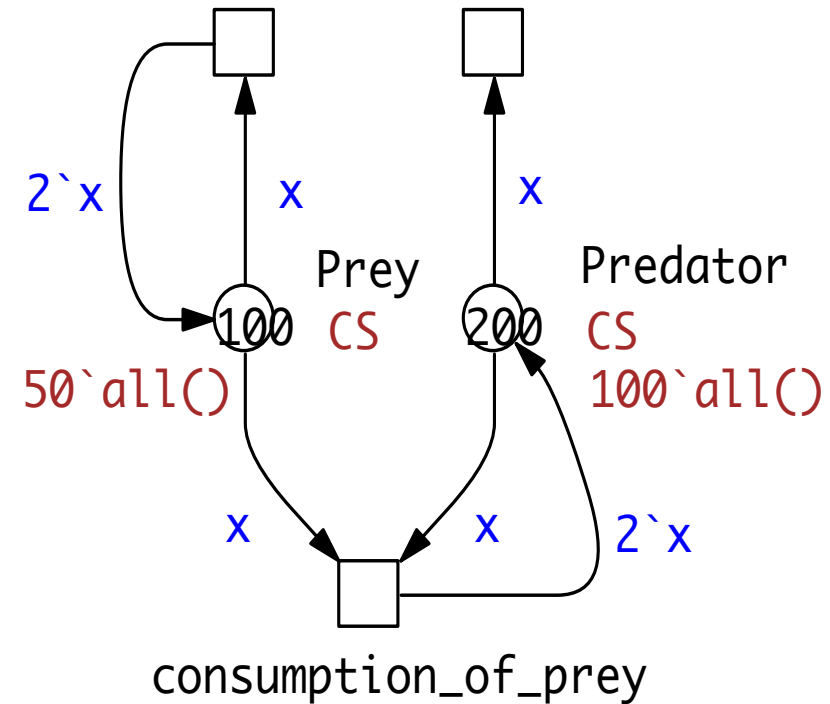
const SIZE = 2;

colourset CS = 1-SIZE;

var x : CS;



reproduction_of_prey predator_death



❑ definitions

colourset CS = 1-2;

var x : CS;

❑ better:

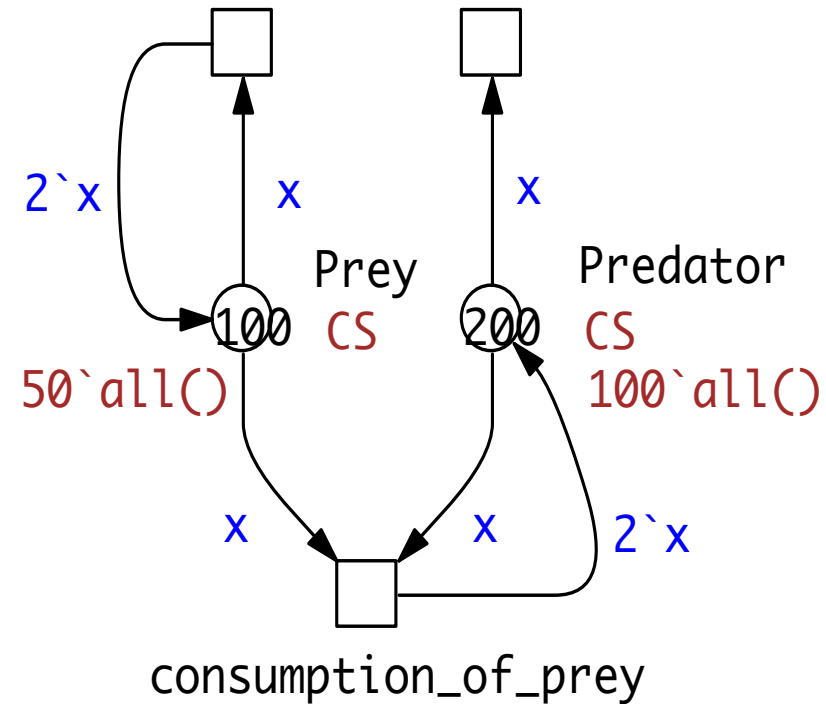
const SIZE = 2;

colourset CS = 1-SIZE;

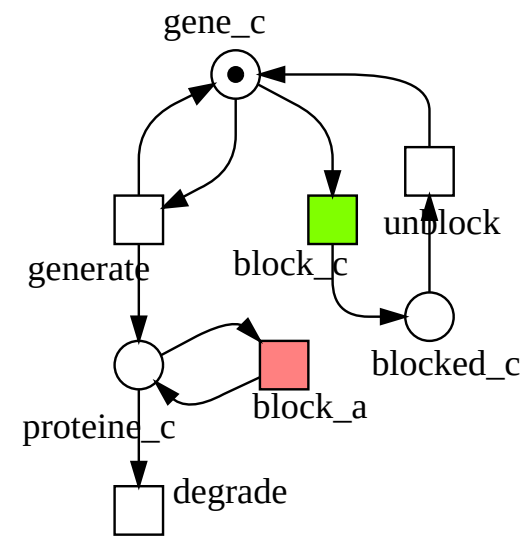
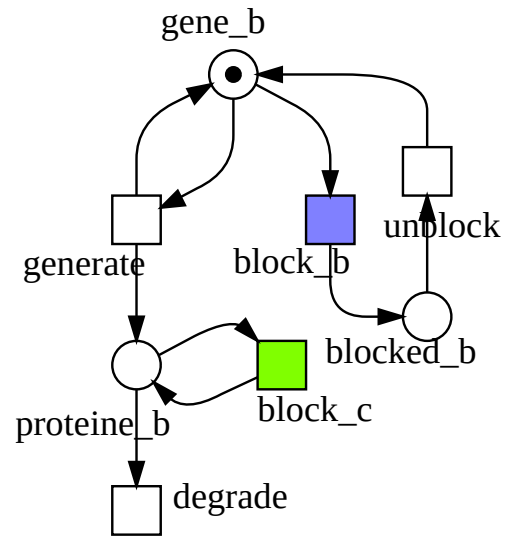
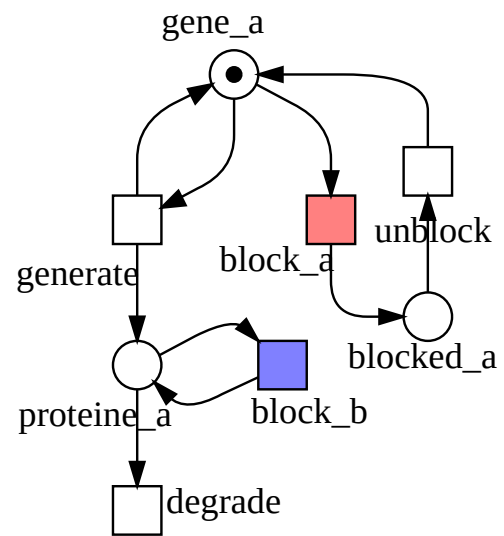
var x : CS;

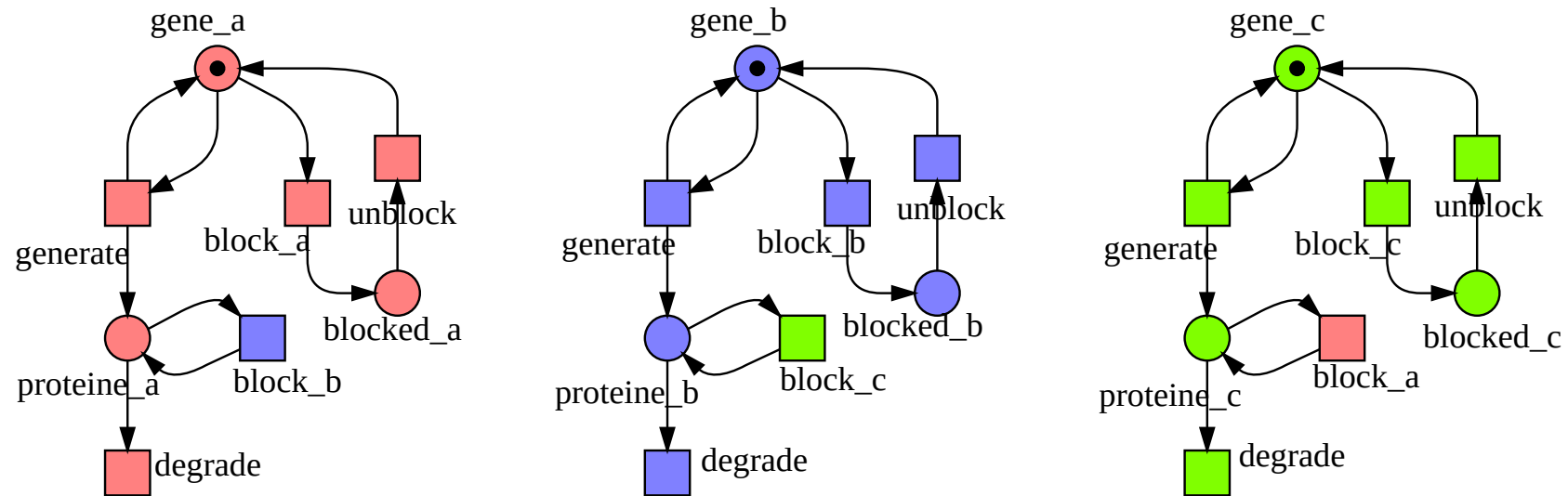


reproduction_of_prey predator_death



❑ changing SIZE adapts the model to various scenarios

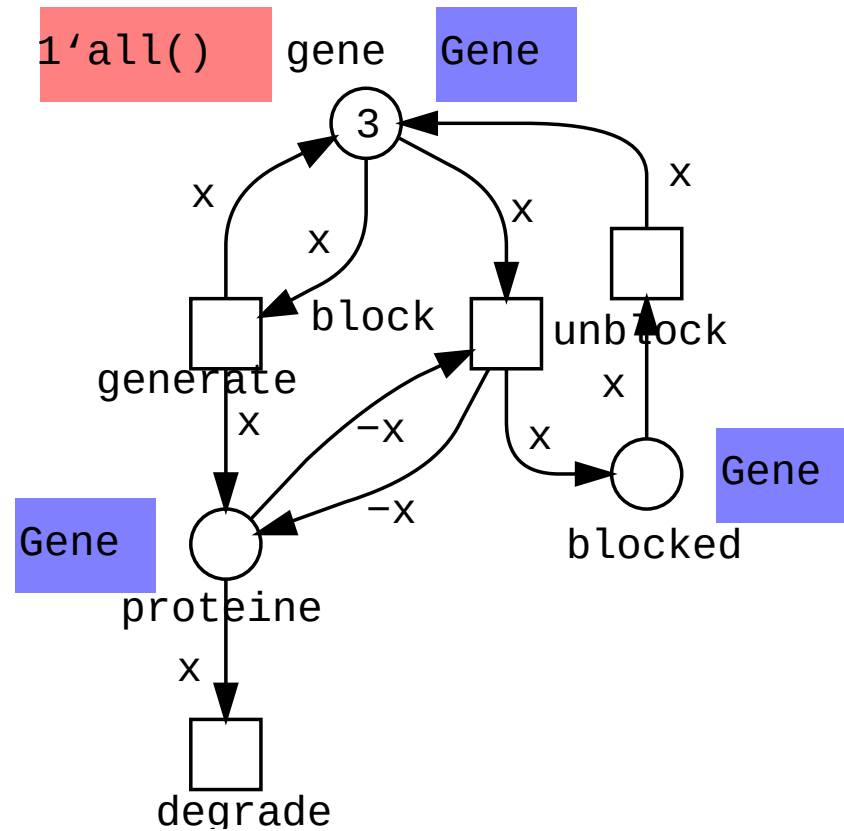




definitions

```
colorset Gene = enum a-c;
```

```
var x : Gene;
```

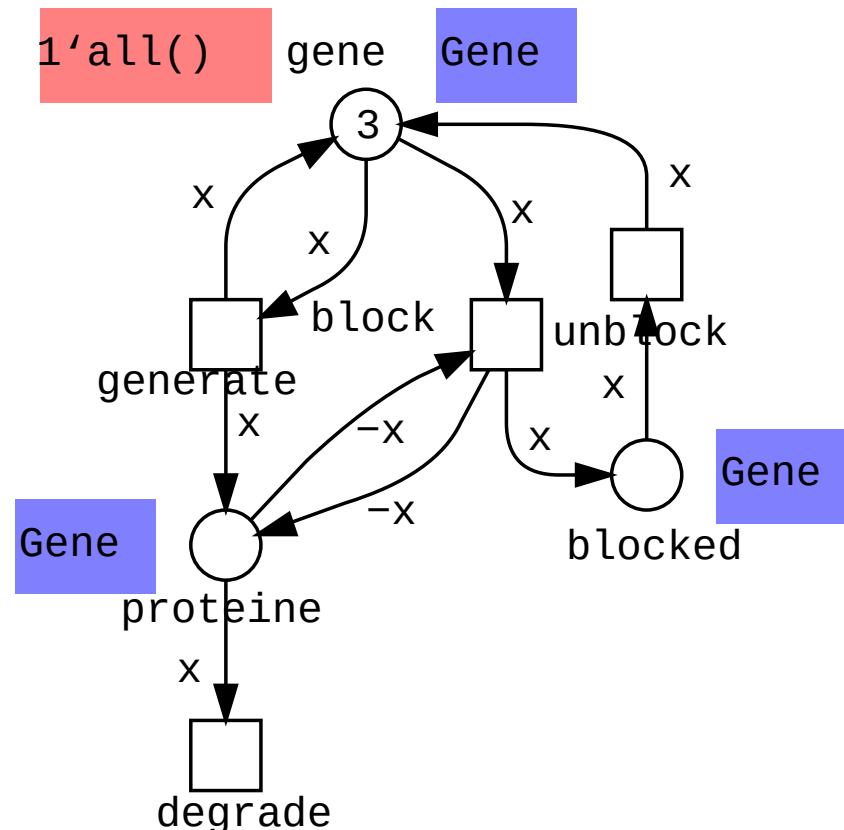
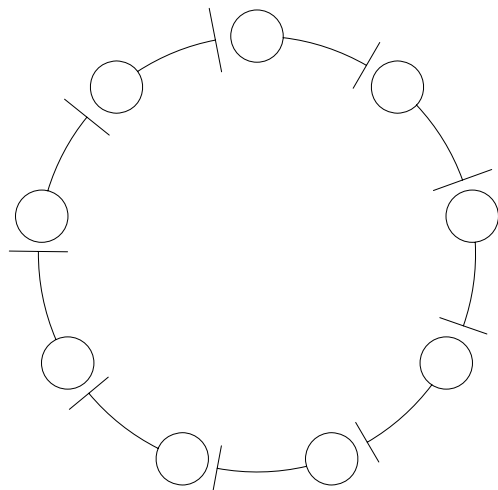


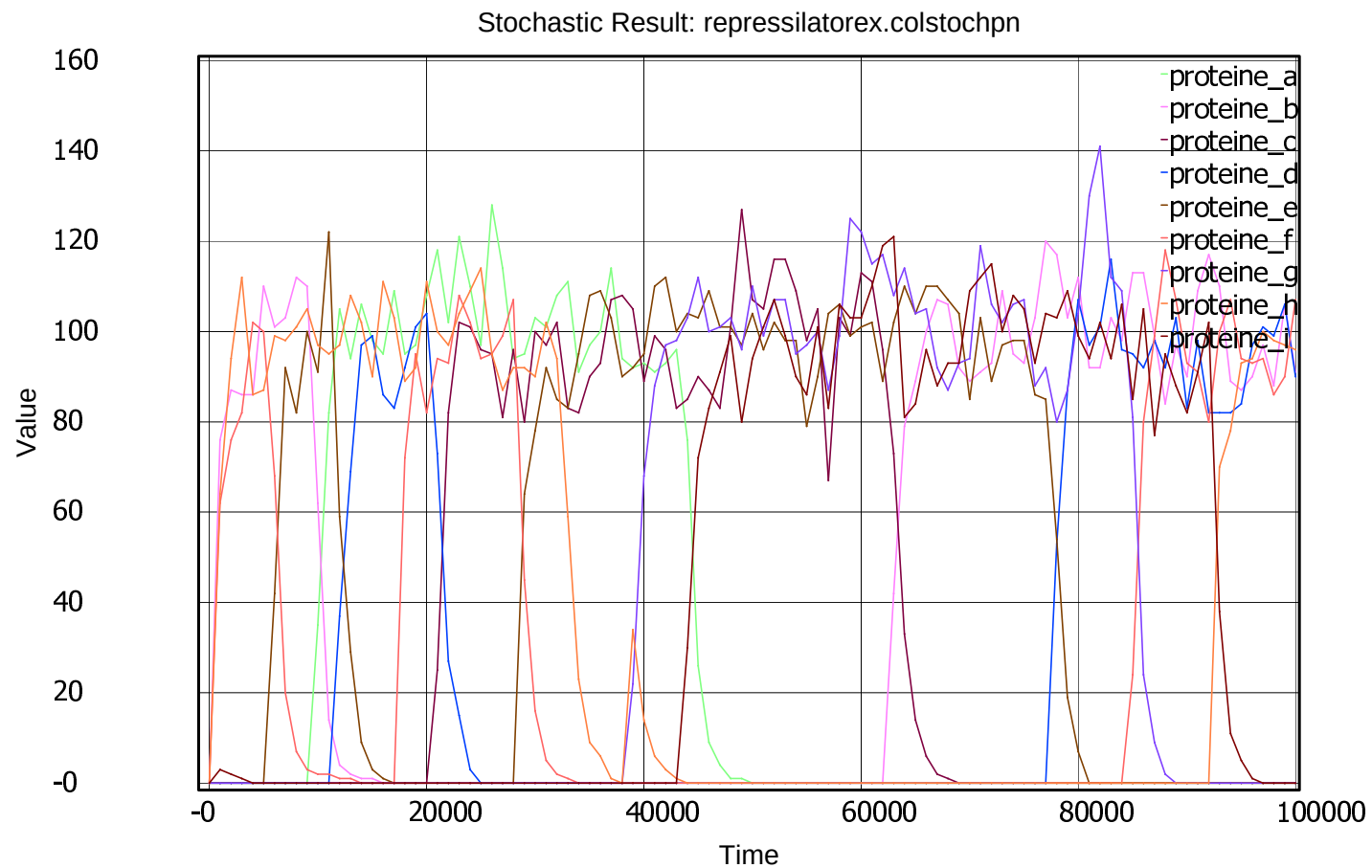
❑ definitions

colorset Gene = enum a-c;
var x : Gene;

❑ model scaling

colorset Gene = enum **a-i**;

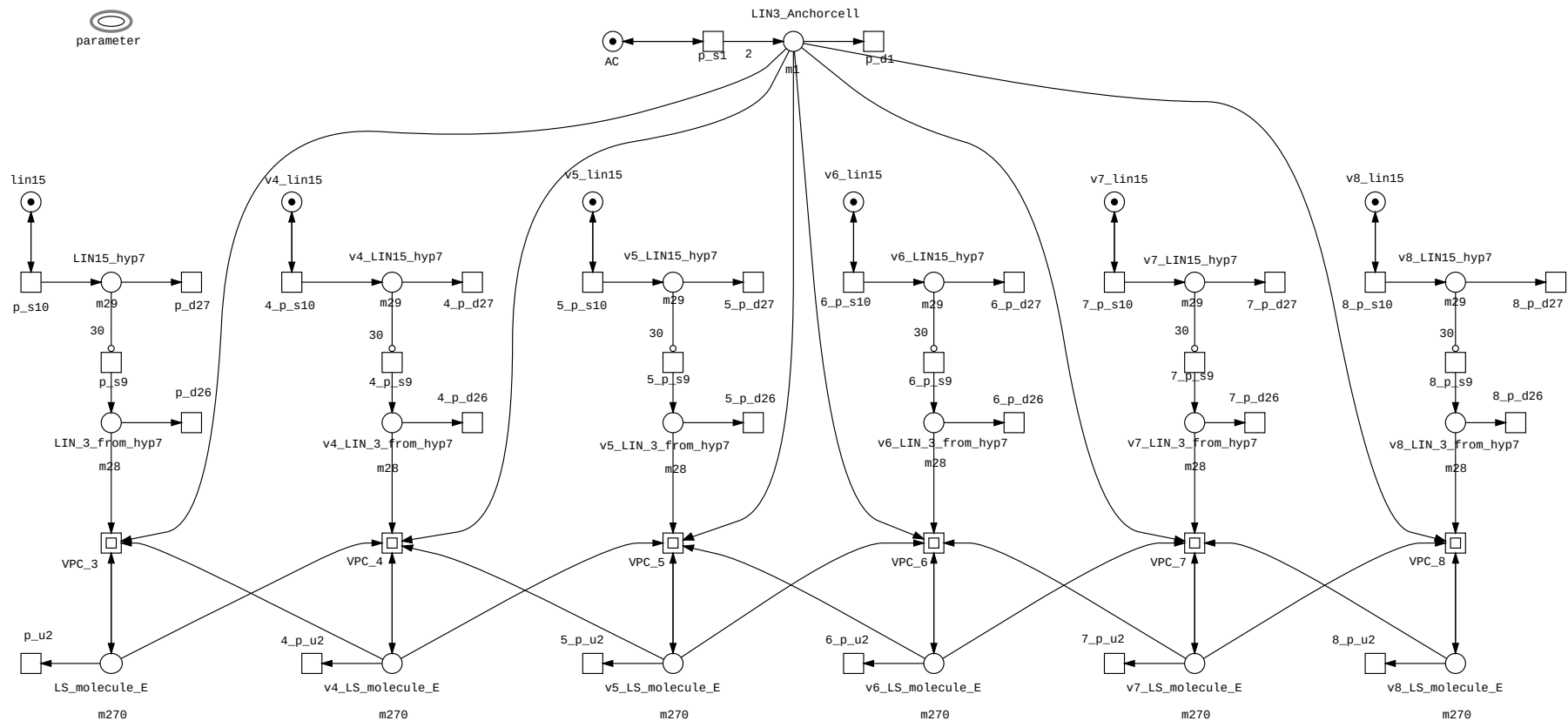




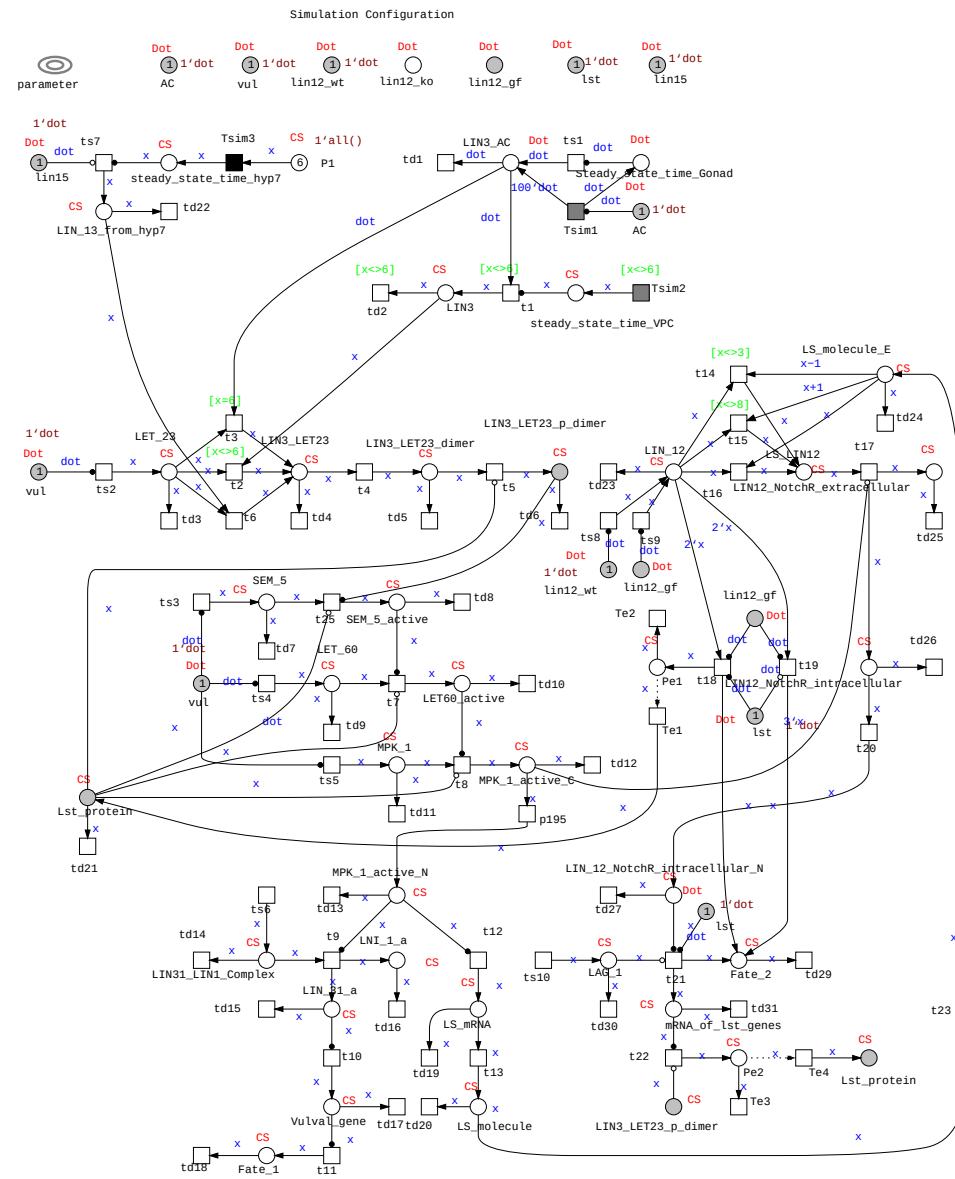
[LI ET AL. 2009]

[BONZANNI ET AL. 2009]

PLACES: 206
TRANSITIONS: 366

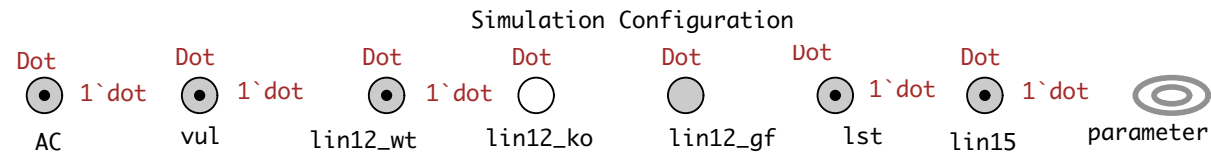


Ex: C. ELEGANS, COLOURED

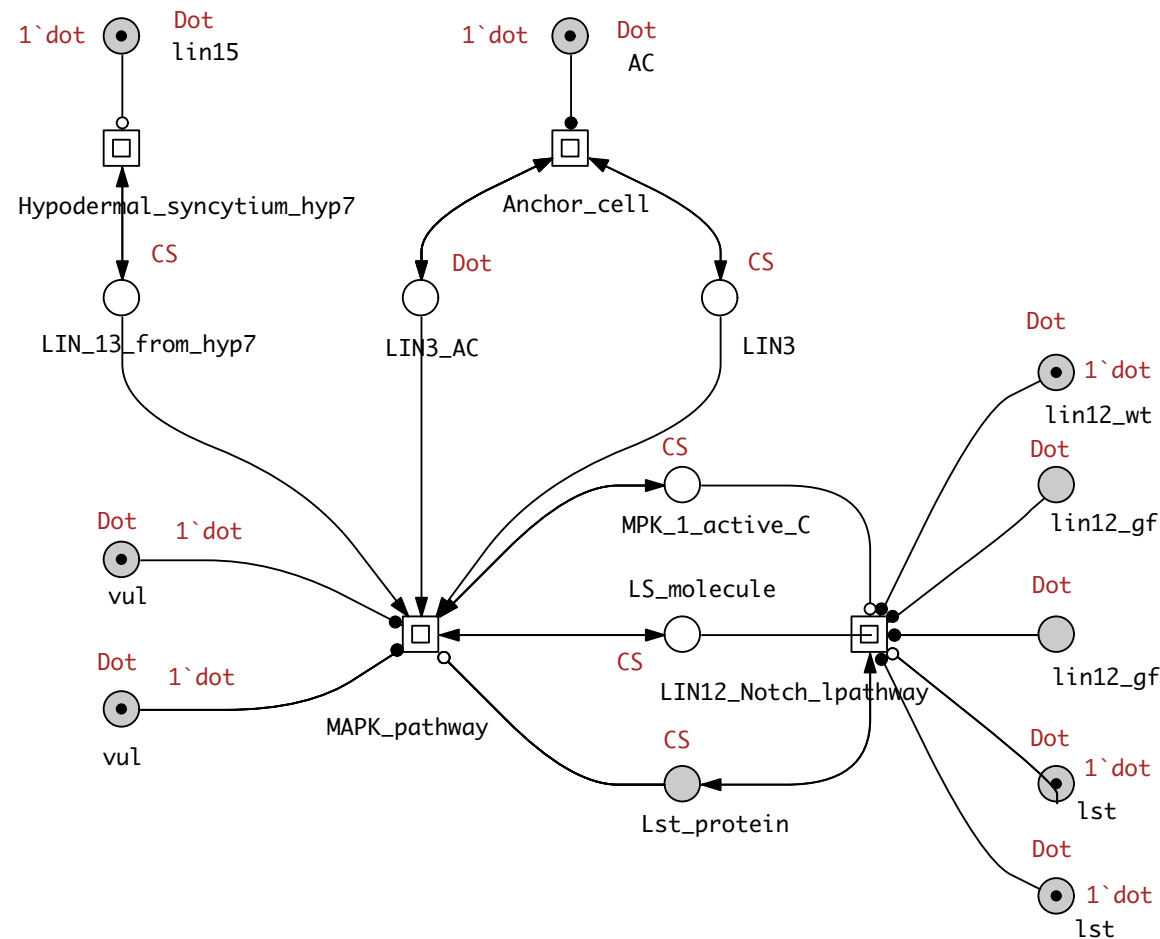


PLACES: 44
TRANSITIONS: 72

Ex: C. ELEGANS, COLOURED & HIERARCHIES



PLACES: 44
TRANSITIONS: 72



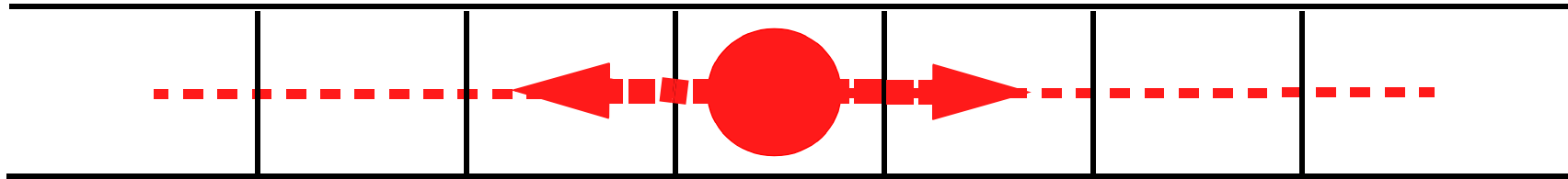
COLOURING SPACE

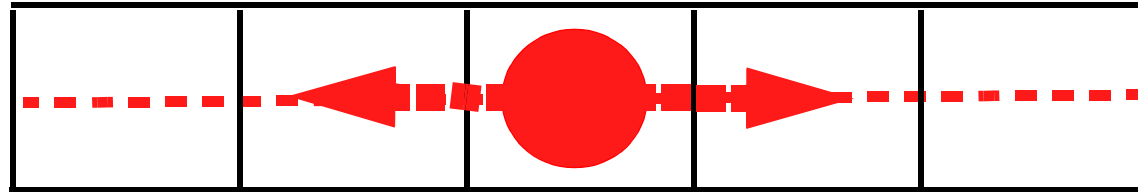
EXAMPLE 1:

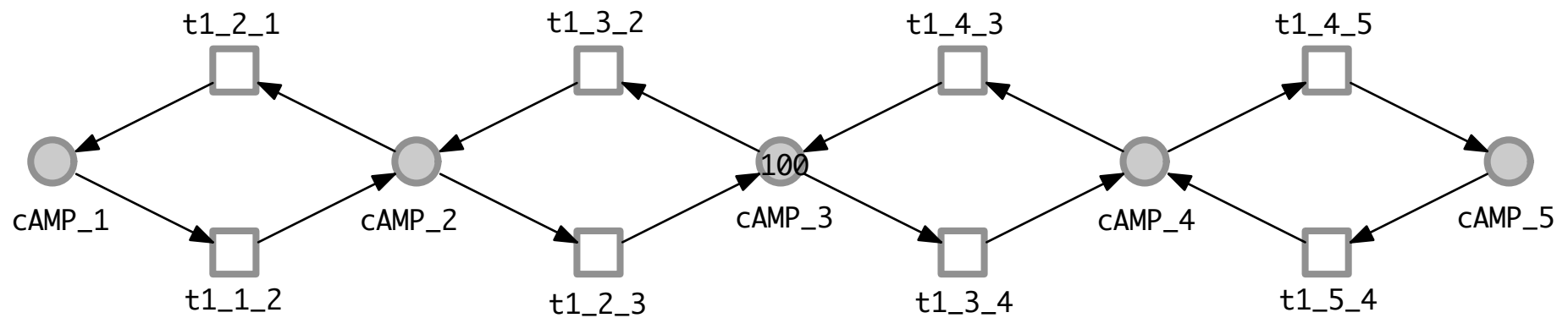
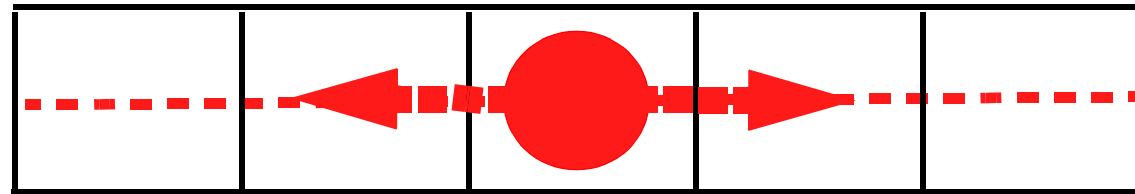
DIFFUSION IN SPACE



Richmond, 13/09/2011







❑ definitions

const *D1* = 5; *// grid size*

const *MIDDLE* = *D1*/2;

colorset *CS* = 1-*D1*; *// grid positions*

var *x,y* : *CS*;

❑ definitions

const *D1* = 5; *// grid size*

const *MIDDLE* = *D1*/2;

colorset *CS* = 1-*D1*; *// grid positions*

var *x,y* : *CS*;

function *neighbour1D* (*CS x,a*) **bool**:

// a is neighbour of x

(*a=x-1* | *a=x+1*) & (*1<=a*) & (*a<=D1*);

❑ definitions

const *D1* = 5; *// grid size*

const *MIDDLE* = *D1*/2;

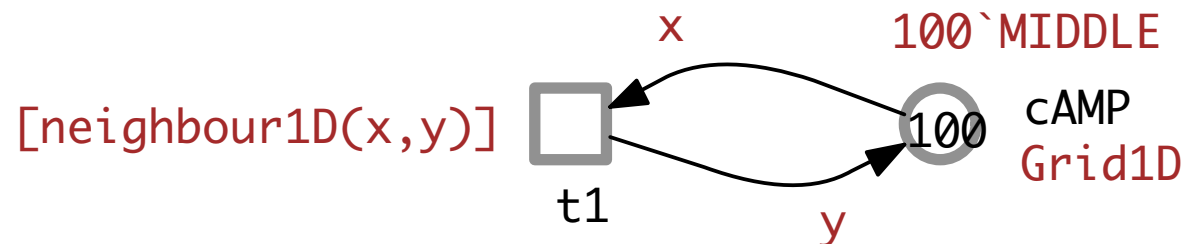
colorset *CS* = 1-*D1*; *// grid positions*

var *x,y* : *CS*;

function *neighbour1D* (*CS* *x,a*) **bool**:

// a is neighbour of x

(*a*=*x*-1 | *a*=*x*+1) & (1<=*a*) & (*a*<=*D1*);



❑ definitions

const *D1* = 5; *// grid size*

const *MIDDLE* = *D1*/2;

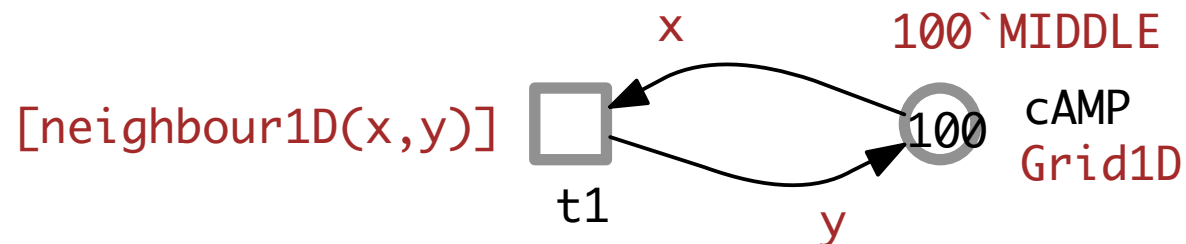
colorset *CS* = 1-*D1*; *// grid positions*

var *x,y* : *CS*;

function *neighbour1D* (*CS* *x,a*) **bool**:

// a is neighbour of x

(*a*=*x*-1 | *a*=*x*+1) & (1<=*a*) & (*a*<=*D1*);



❑ movement = changing colour

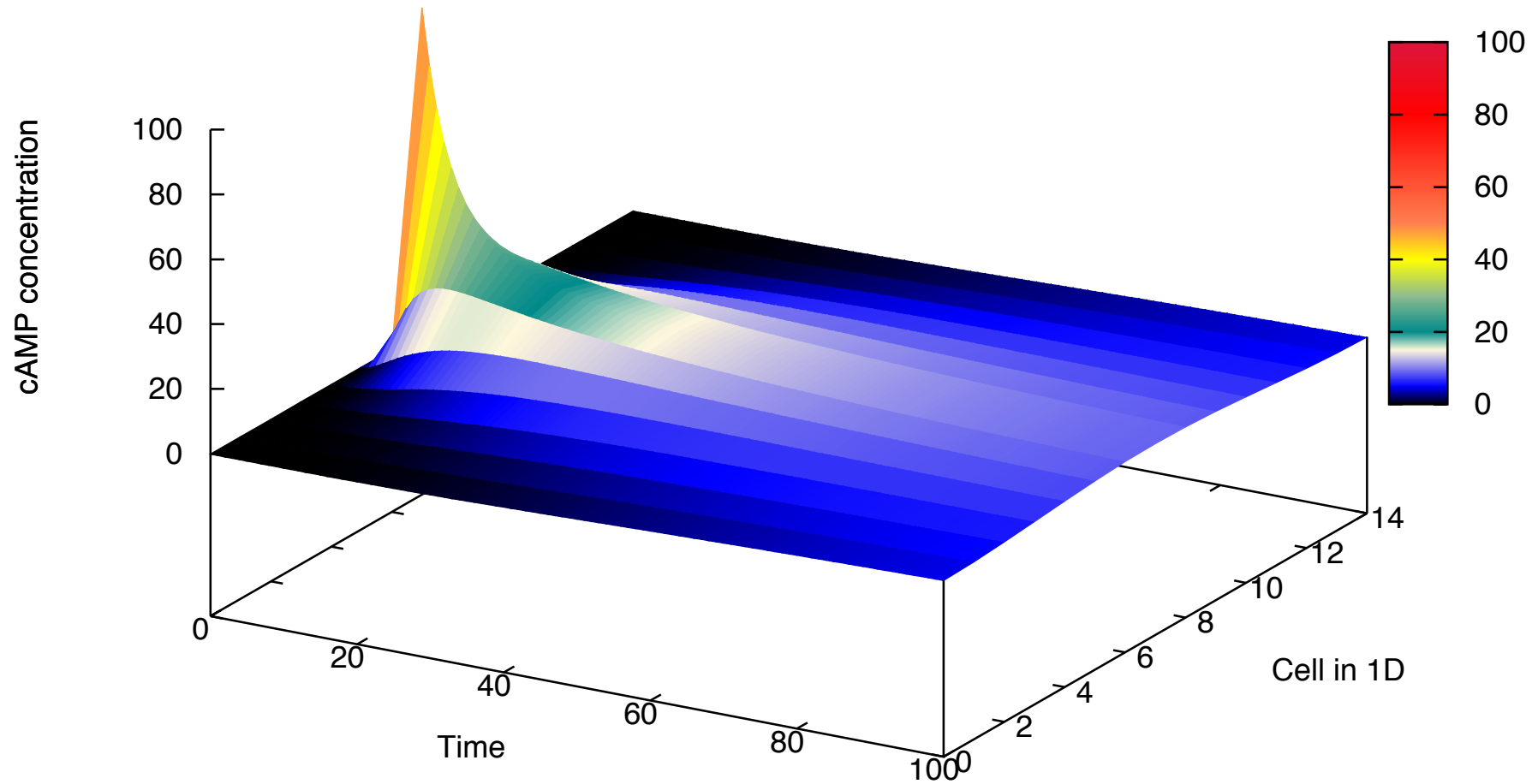
$$\frac{dc_1}{dt} = k \cdot c_2 - k \cdot c_1$$

$$\frac{dc_2}{dt} = k \cdot c_1 + k \cdot c_3 - 2 \cdot k \cdot c_2$$

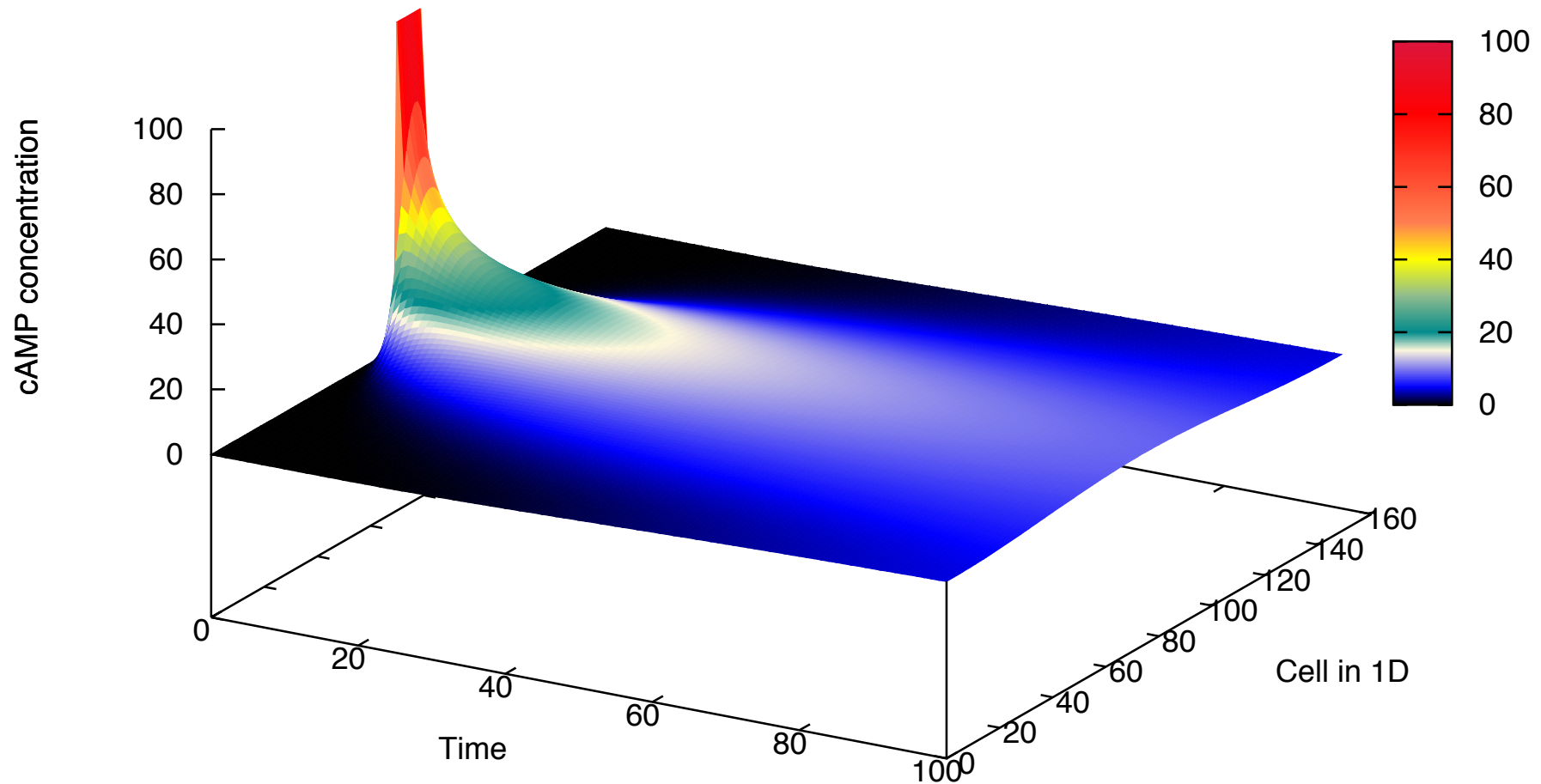
$$\frac{dc_3}{dt} = k \cdot c_2 + k \cdot c_4 - 2 \cdot k \cdot c_3$$

$$\frac{dc_4}{dt} = k \cdot c_3 + k \cdot c_5 - 2 \cdot k \cdot c_4$$

$$\frac{dc_5}{dt} = k \cdot c_4 - k \cdot c_5$$

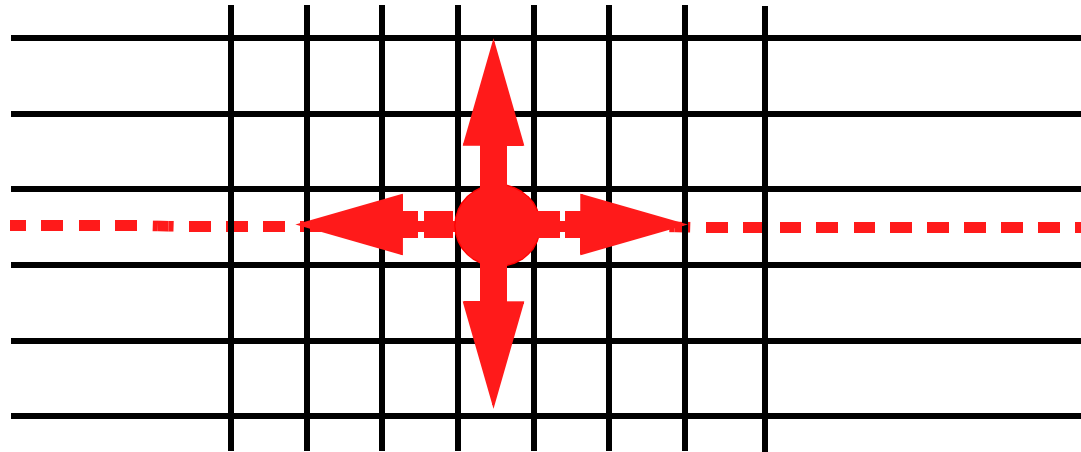


15 GRID POSITIONS

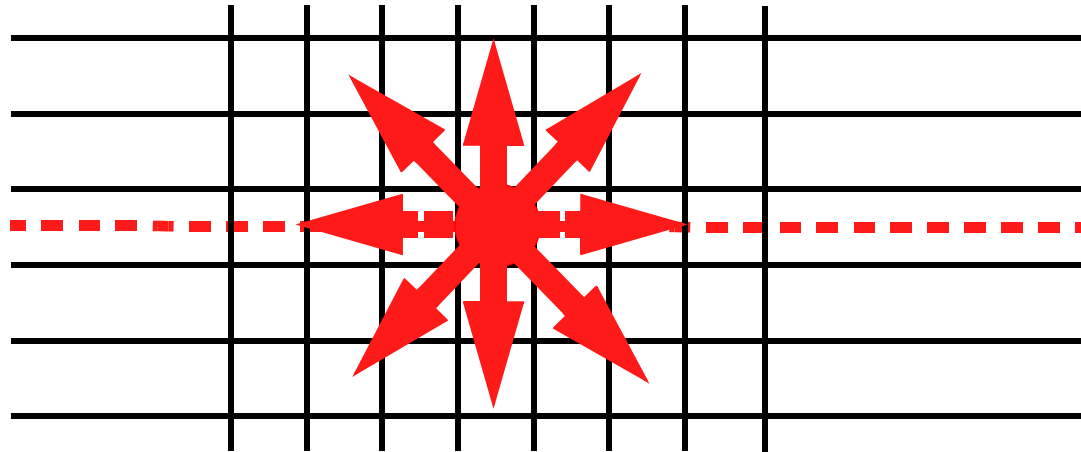


150 GRID POSITIONS, SCALING OF INITIAL MARKING AND RATES

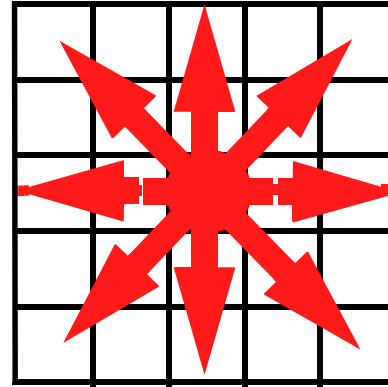
❏ SCHEME



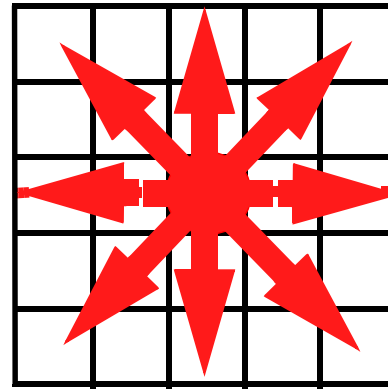
❏ SCHEME



❏ SCHEME



❑ SCHEME



❑ definitions

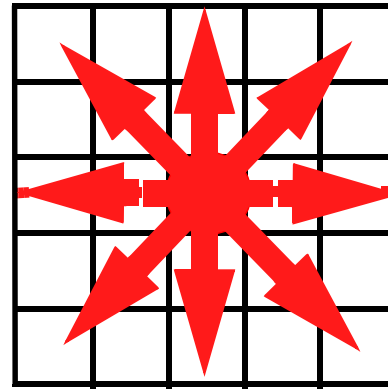
const D1 = 5;

// grid size first dimension

const D2 = D1;

// grid size second dimension

❑ SCHEME



❑ definitions

const D1 = 5;

// grid size first dimension

const D2 = D1;

// grid size second dimension

const MIDDLE = D1/2;

colorset CD1 = 1-D1;

// row index

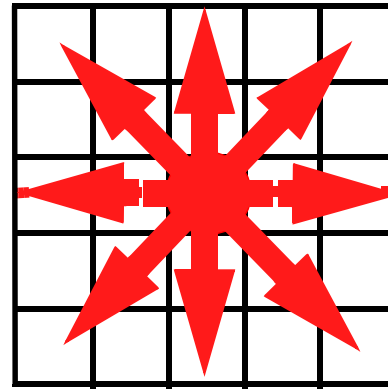
colorset CD2 = 1-D2;

// column index

colorset Grid2D = CD1 x CD2;

// 2D grid

❑ SCHEME



❑ definitions

const D1 = 5;

// grid size first dimension

const D2 = D1;

// grid size second dimension

const MIDDLE = D1/2;

colorset CD1 = 1-D1;

// row index

colorset CD2 = 1-D2;

// column index

colorset Grid2D = CD1 x CD2;

// 2D grid

var x, a : CD1;

var y, b : CD2;

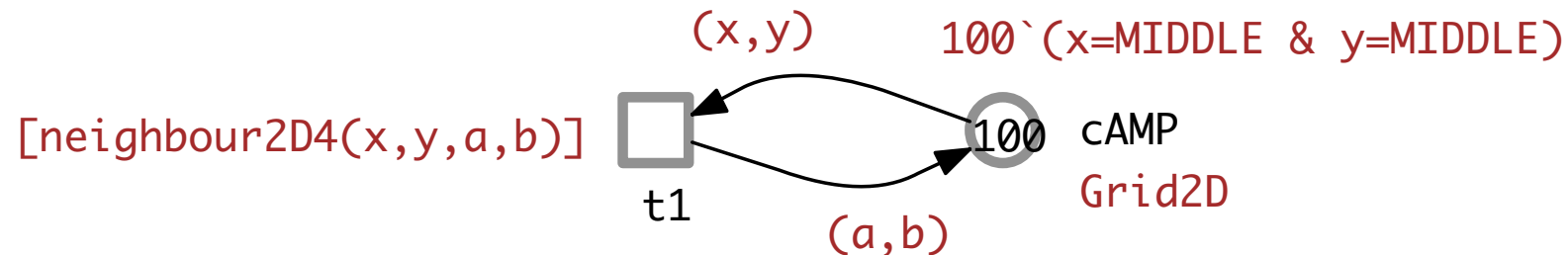
❑ four neighbours

function neighbour2D4 (CD1 x, CD2 y, CD1 a, CD2 b) **bool**:

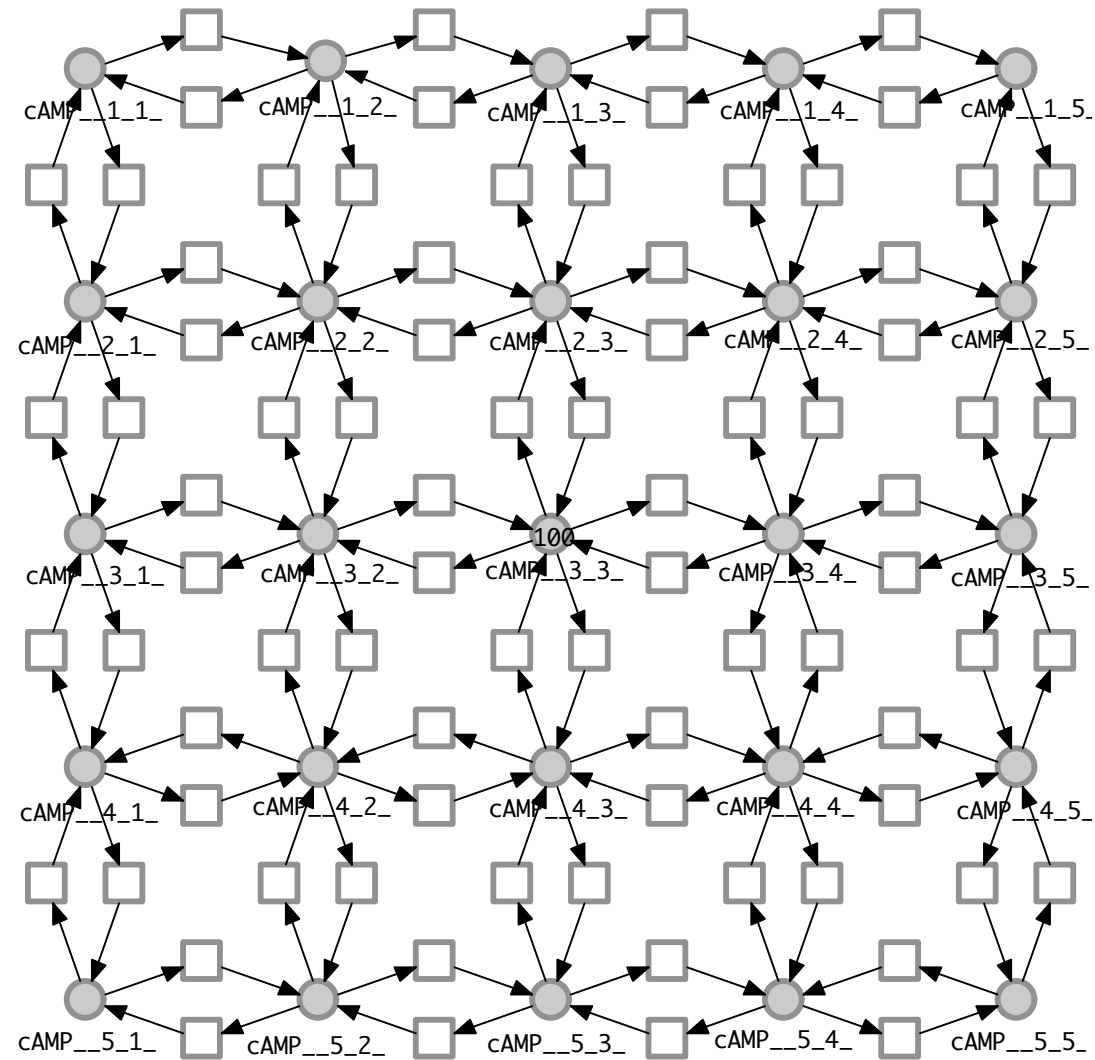
// (a,b) is one of the up to four neighbours of (x,y)

$(a=x \ \& \ b=y-1) \mid (a=x \ \& \ b=y+1)$

$\mid (b=y \ \& \ a=x-1) \mid (b=y \ \& \ a=x+1);$



Ex1: DIFFUSION - 2D4 NEIGHBOURHOOD



❑ eight neighbours

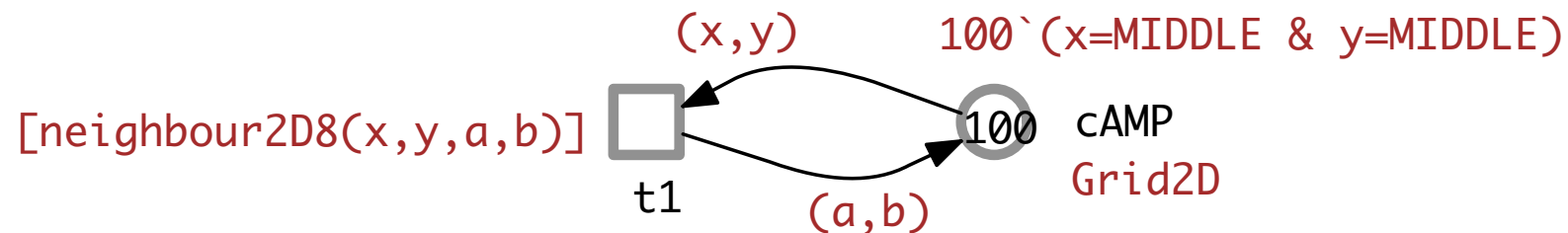
function neighbour2D8 (CD1 x, CD2 y, CD1 a, CD2 b) **bool**:

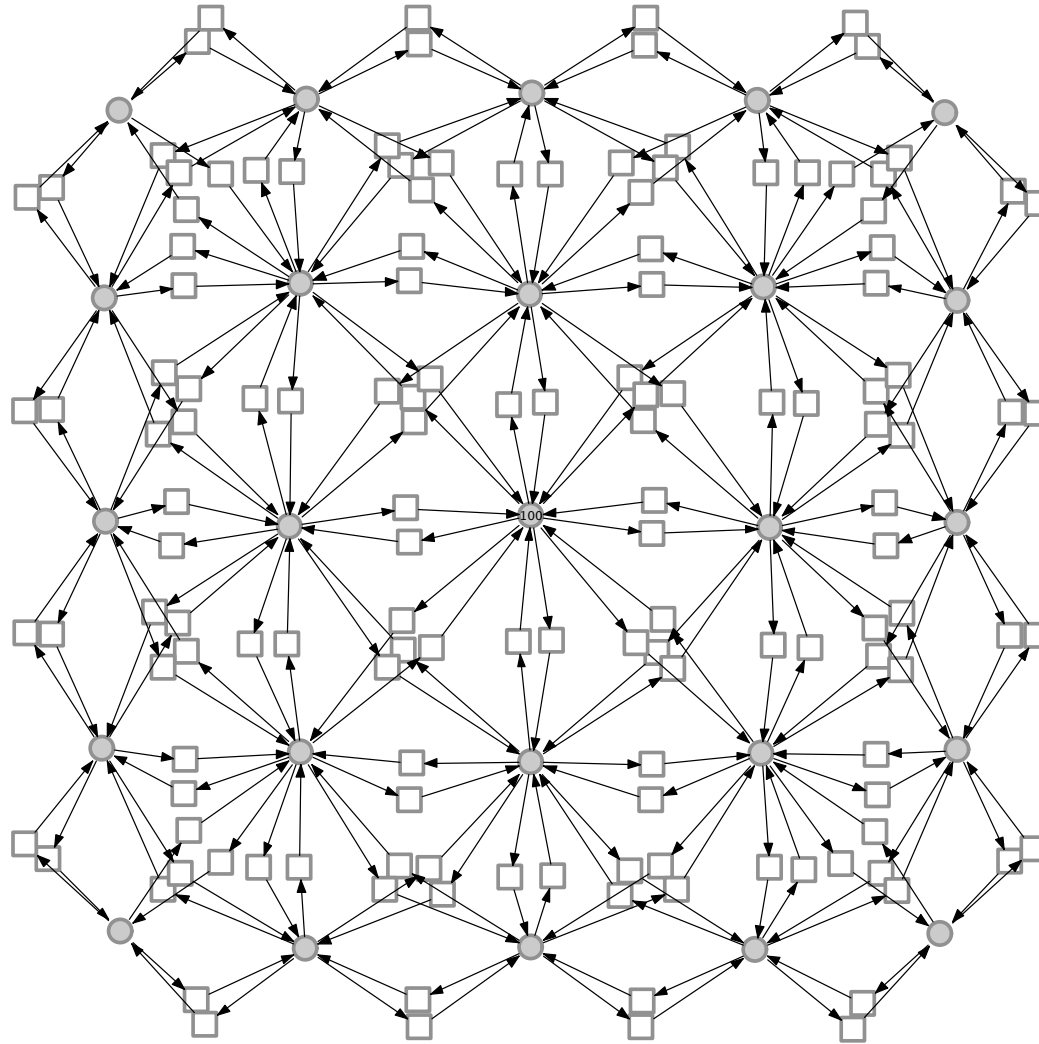
// (a,b) is one of the up to eight neighbours of (x,y)

$(a=x-1 \mid a=x \mid a=x+1) \ \& \ (b = y-1 \mid b=y \mid b=y+1)$

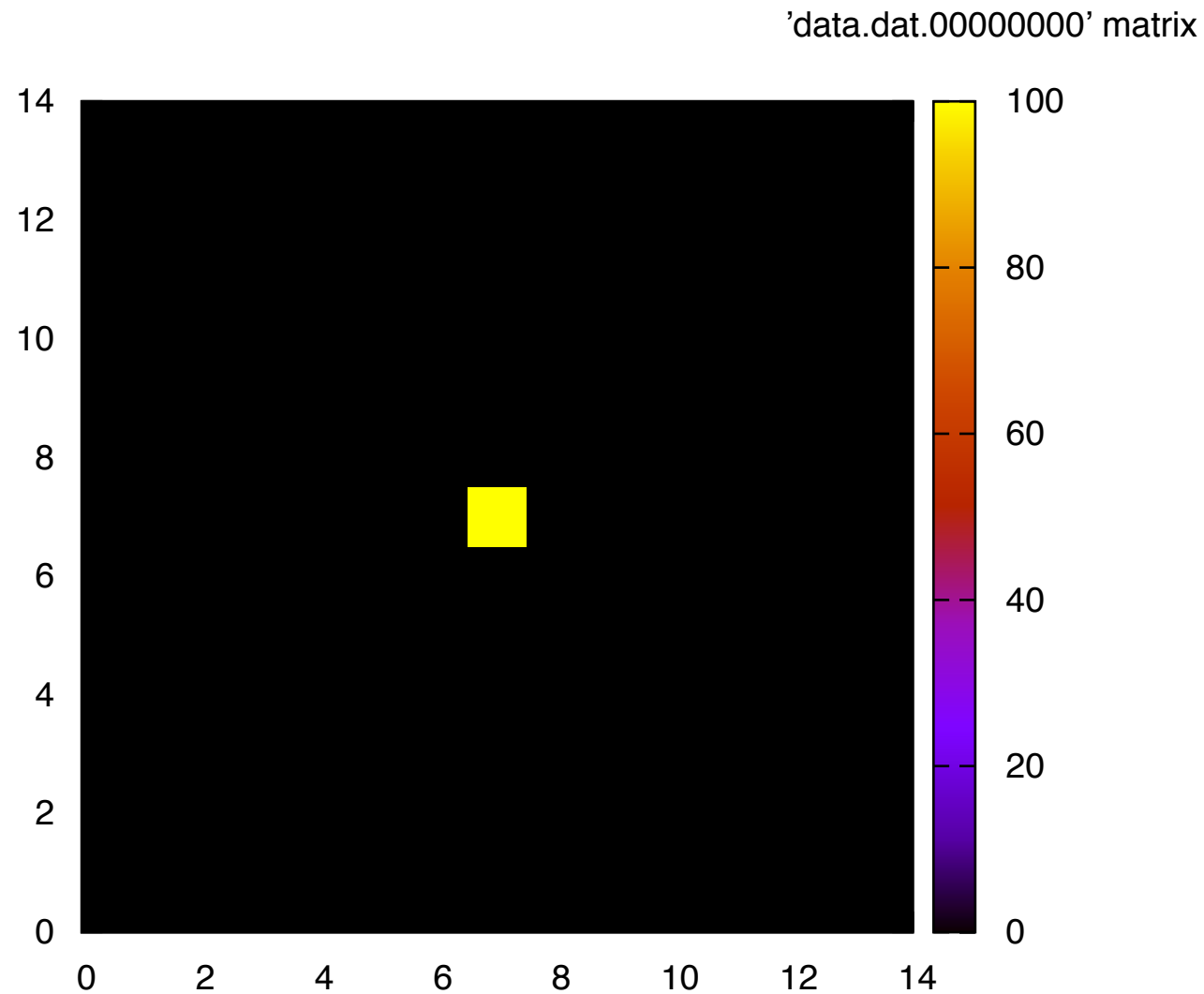
$\& \ !(a=x \ \& \ b=y)$

$\& \ (1 \leq a \ \& \ a \leq D1) \ \& \ (1 \leq b \ \& \ b \leq D2);$

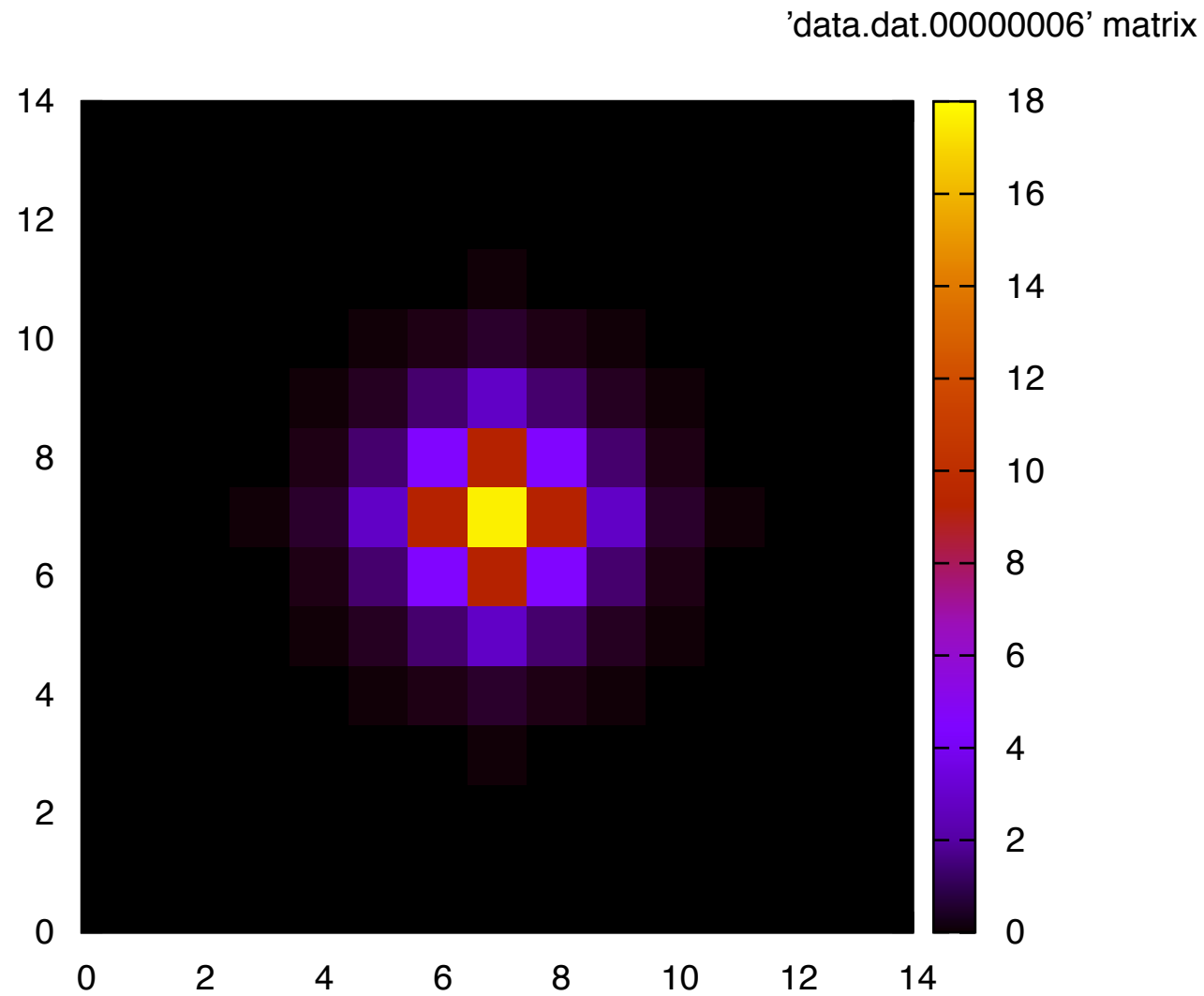




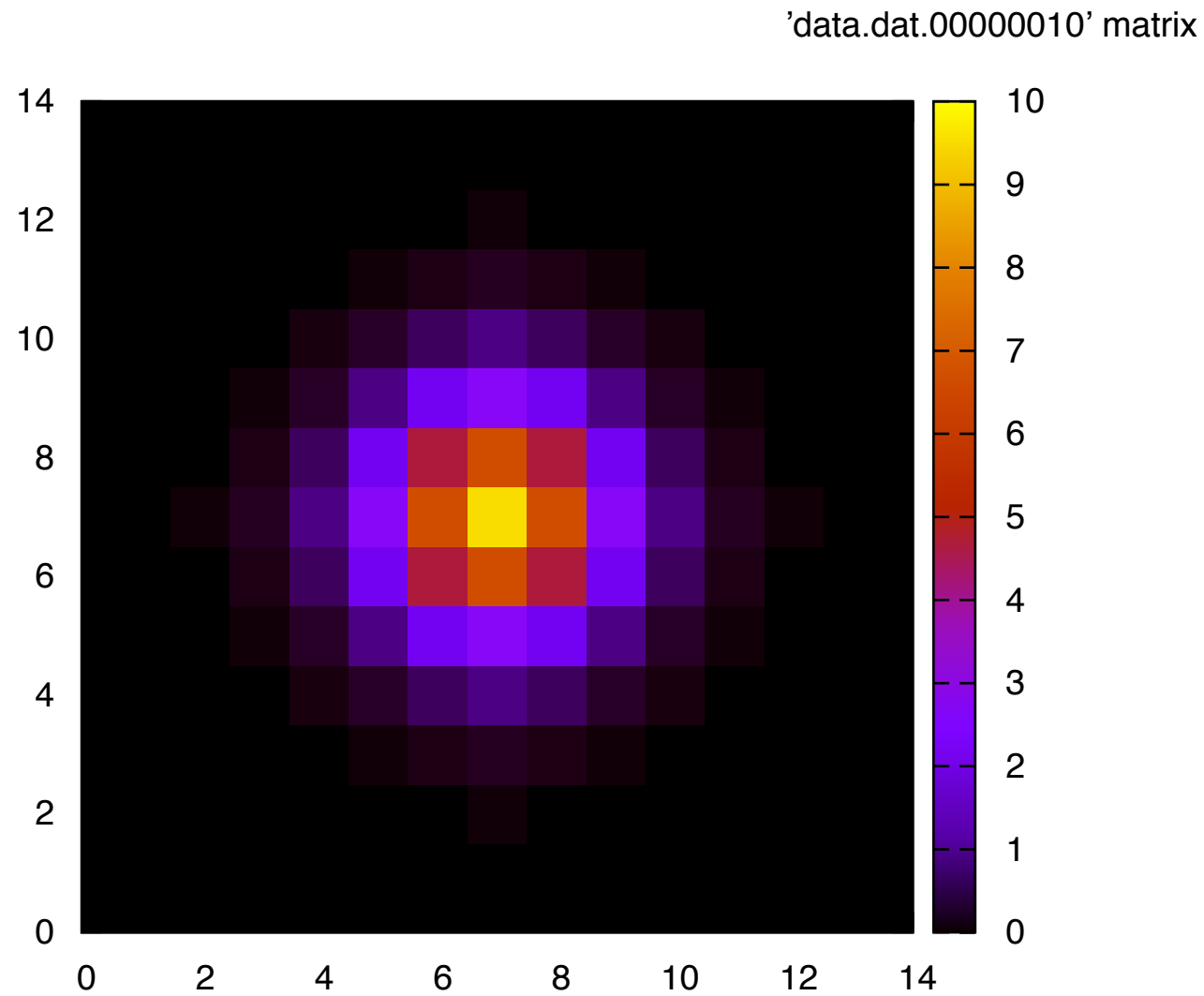
Ex1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



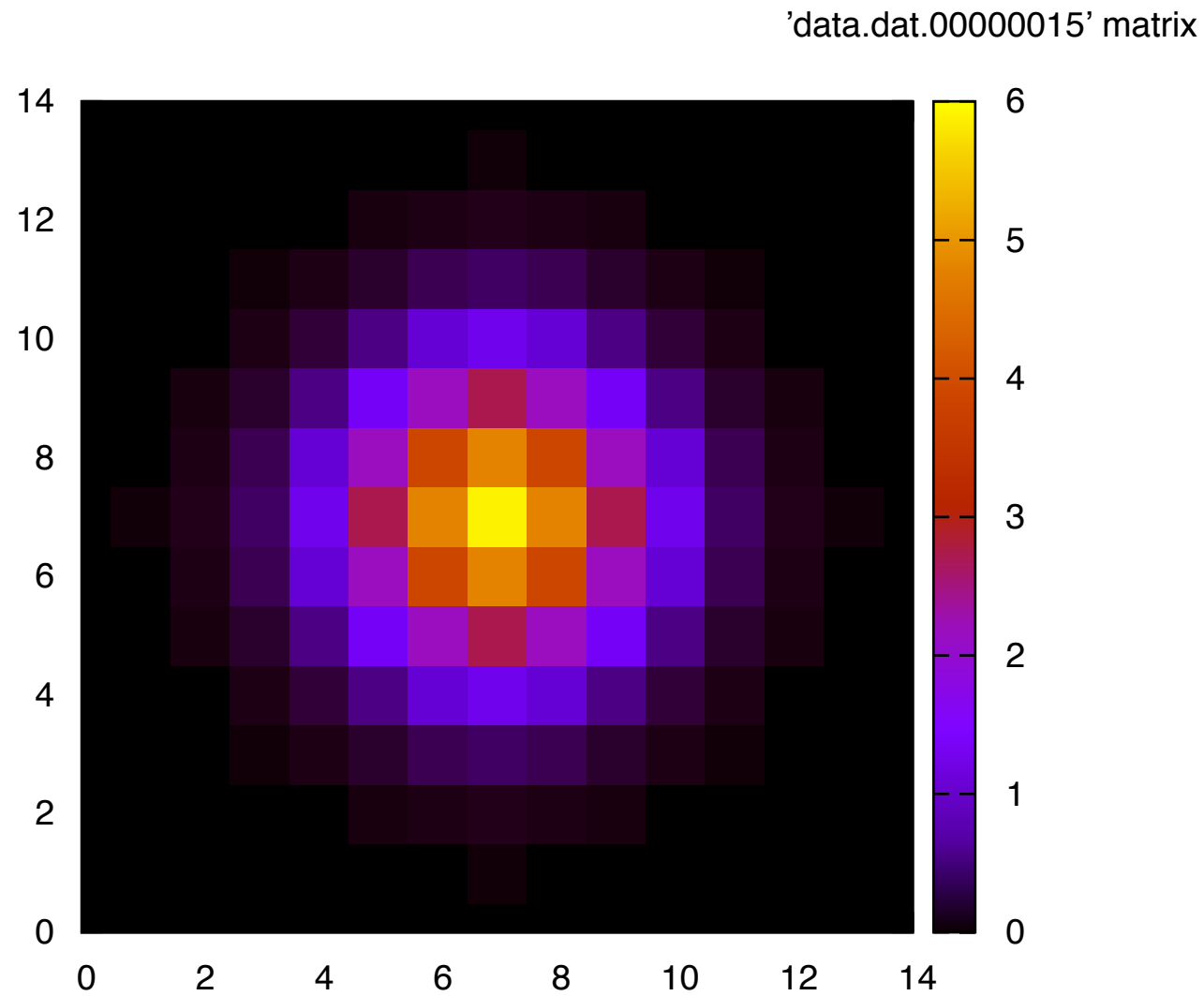
Ex1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



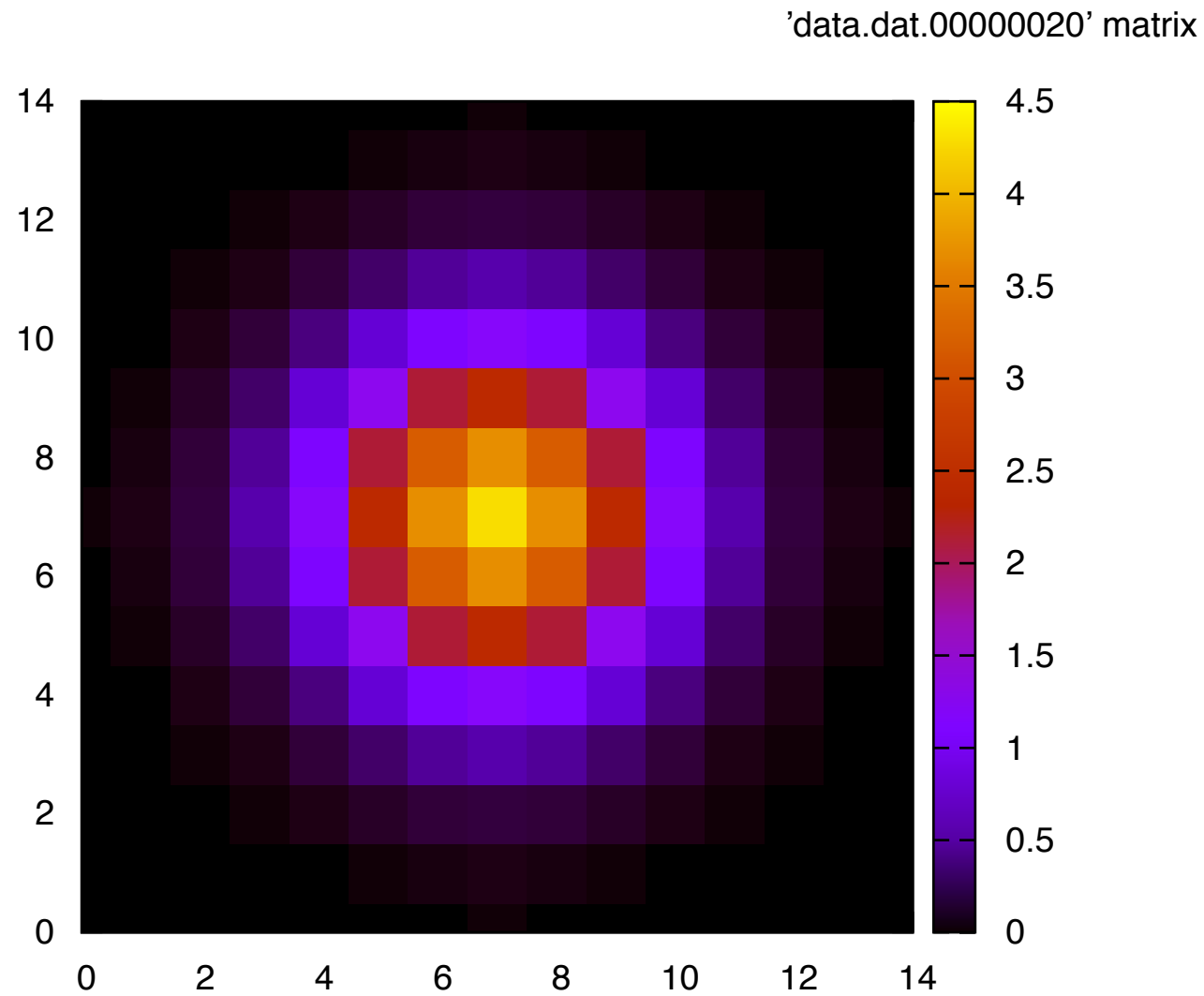
Ex1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



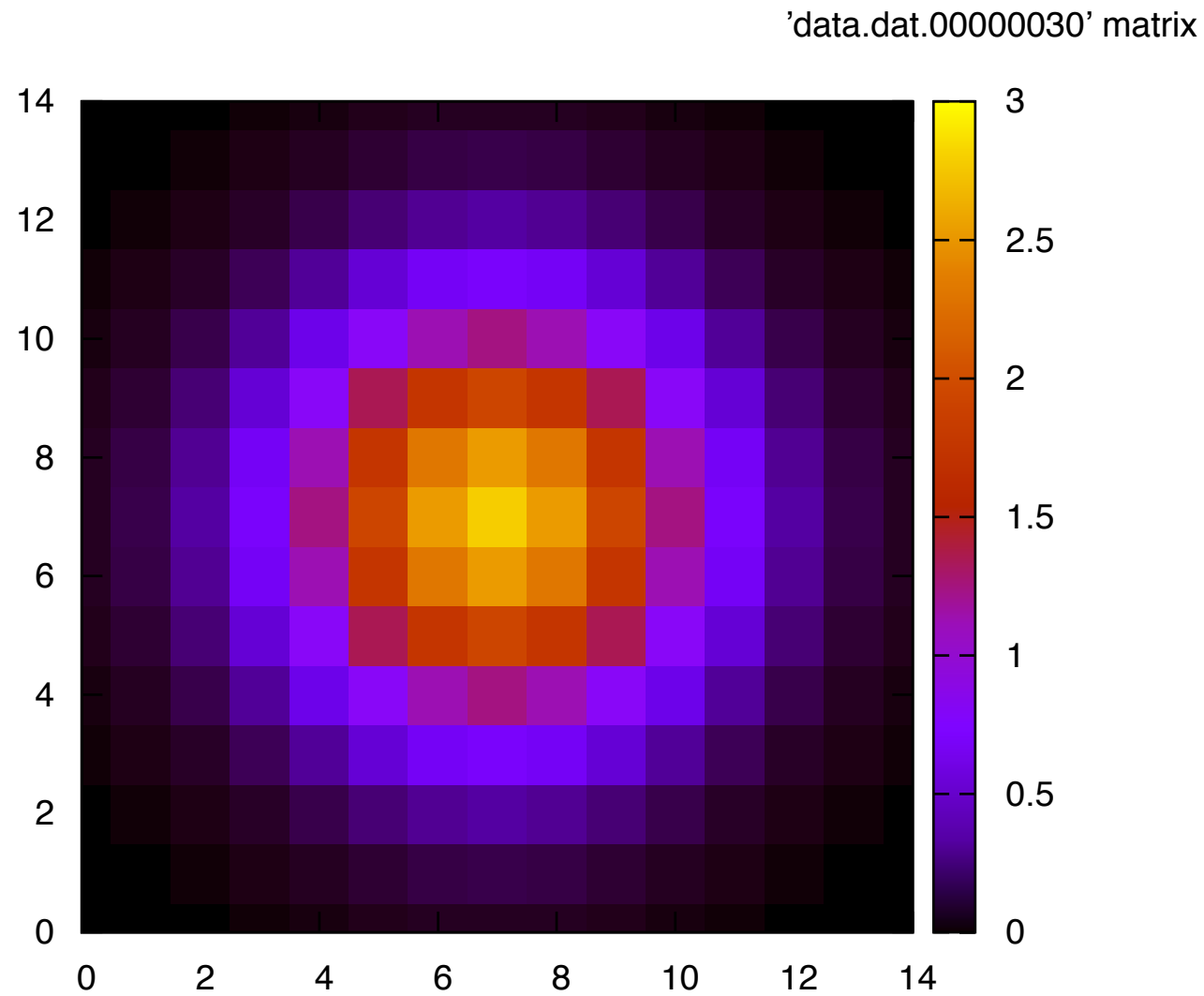
Ex1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15



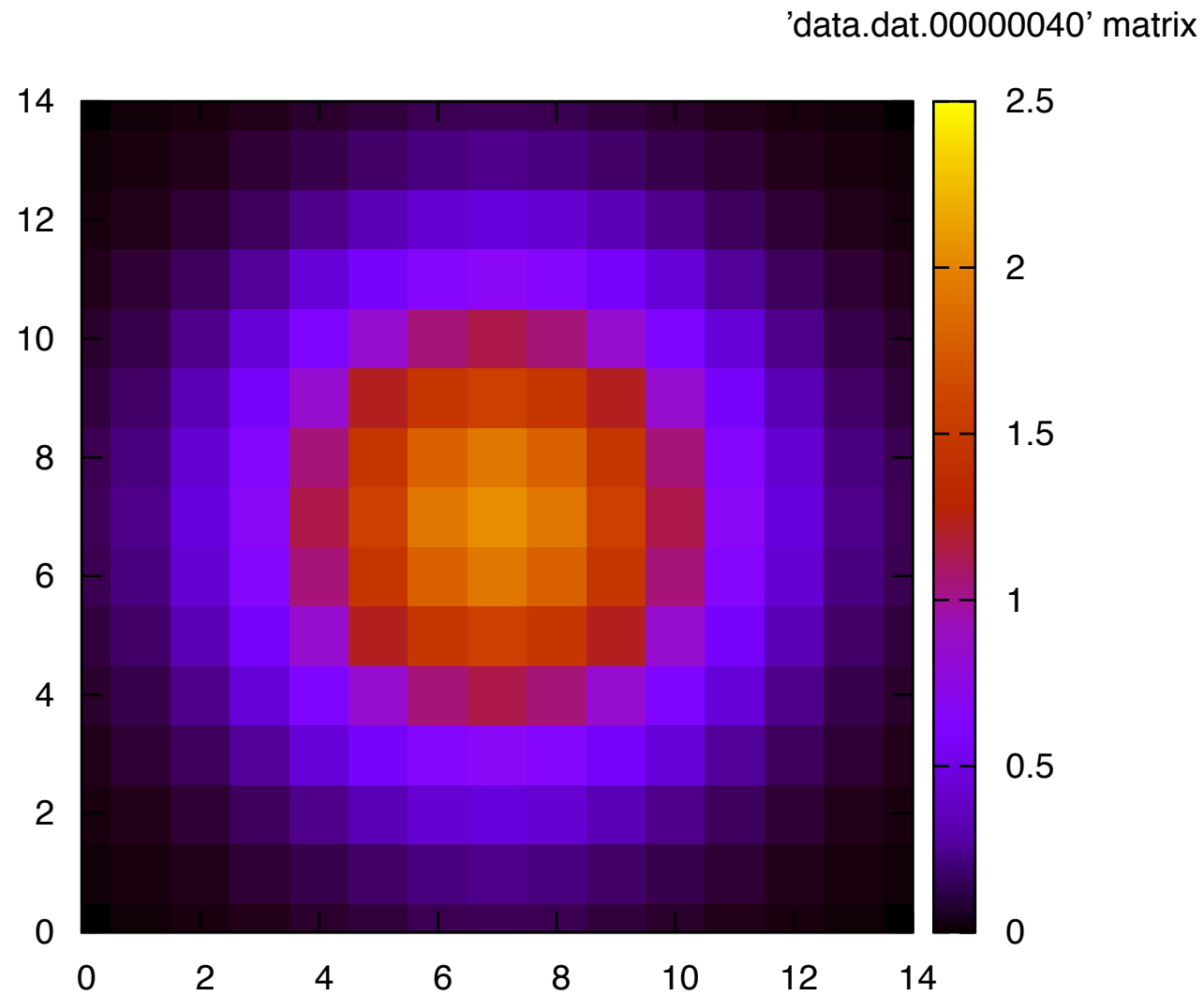
Ex1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15

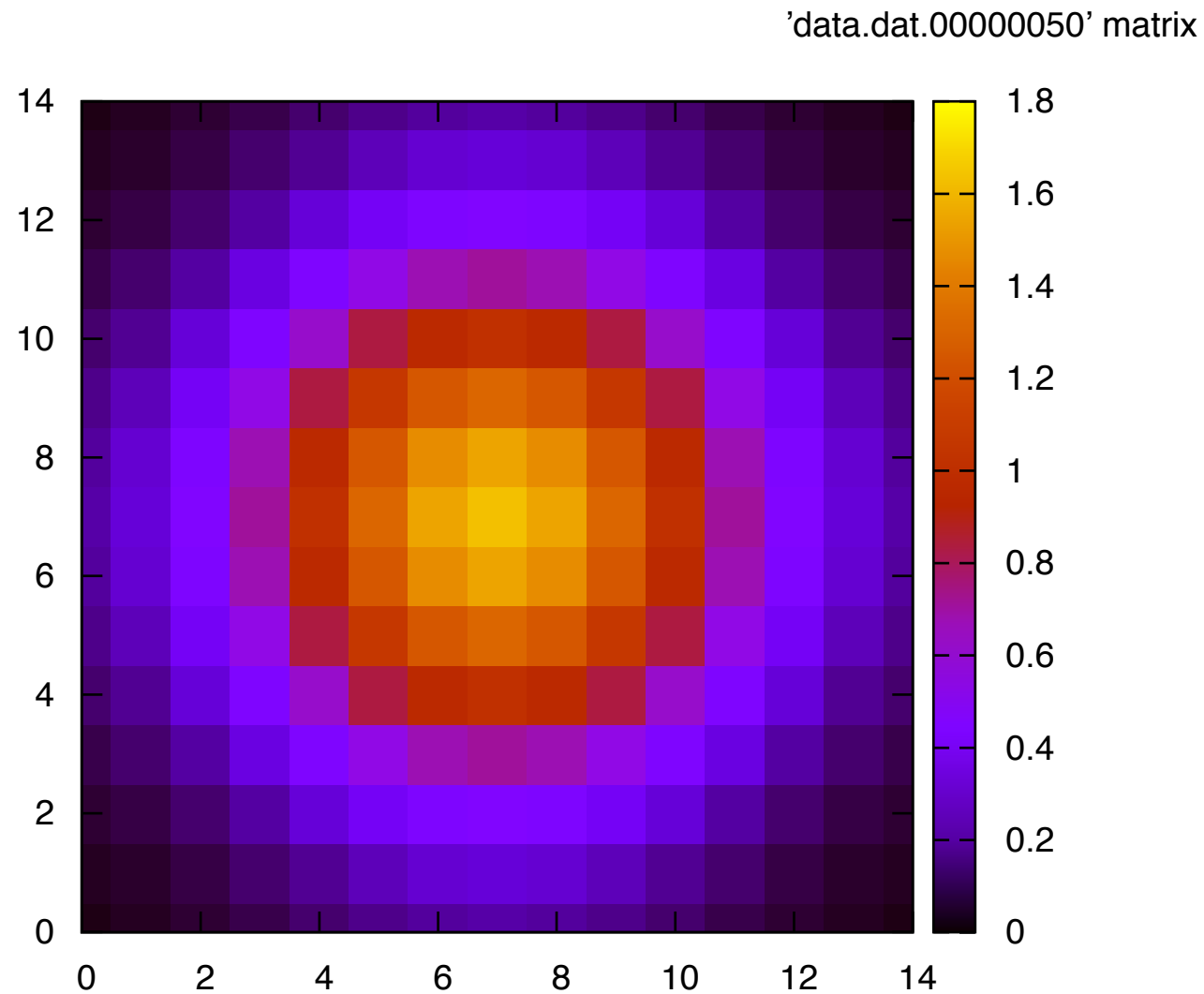


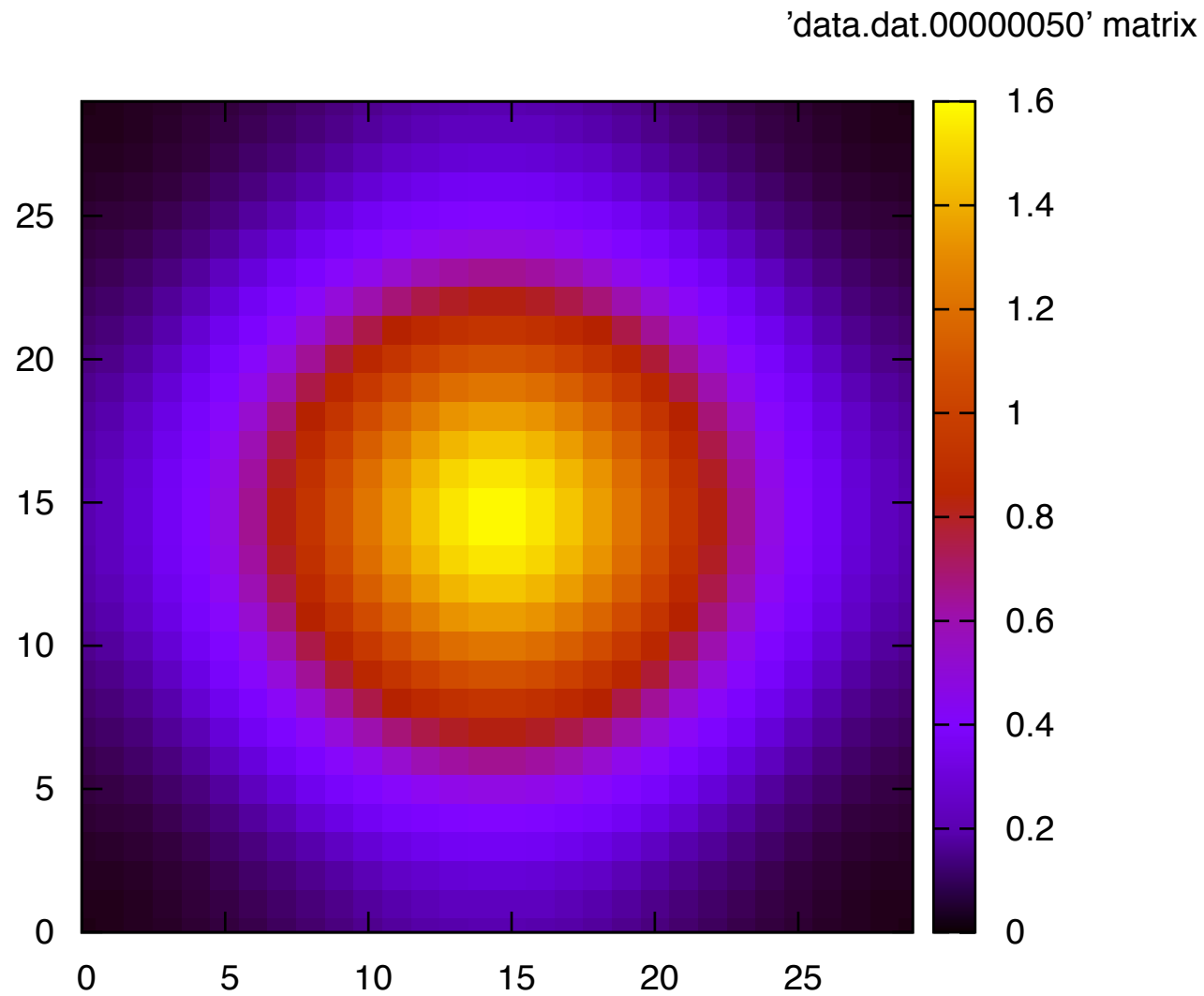
Ex1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15

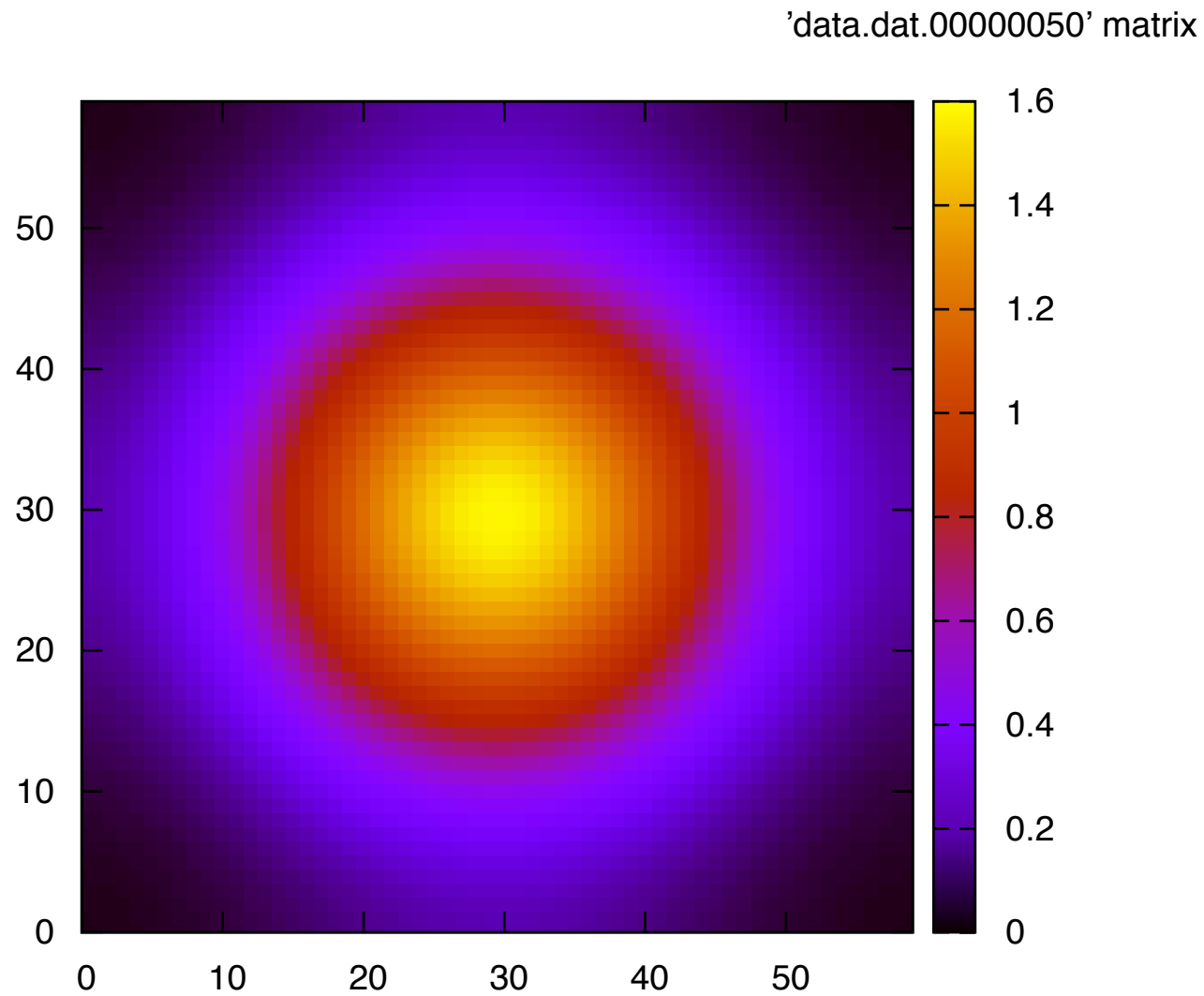


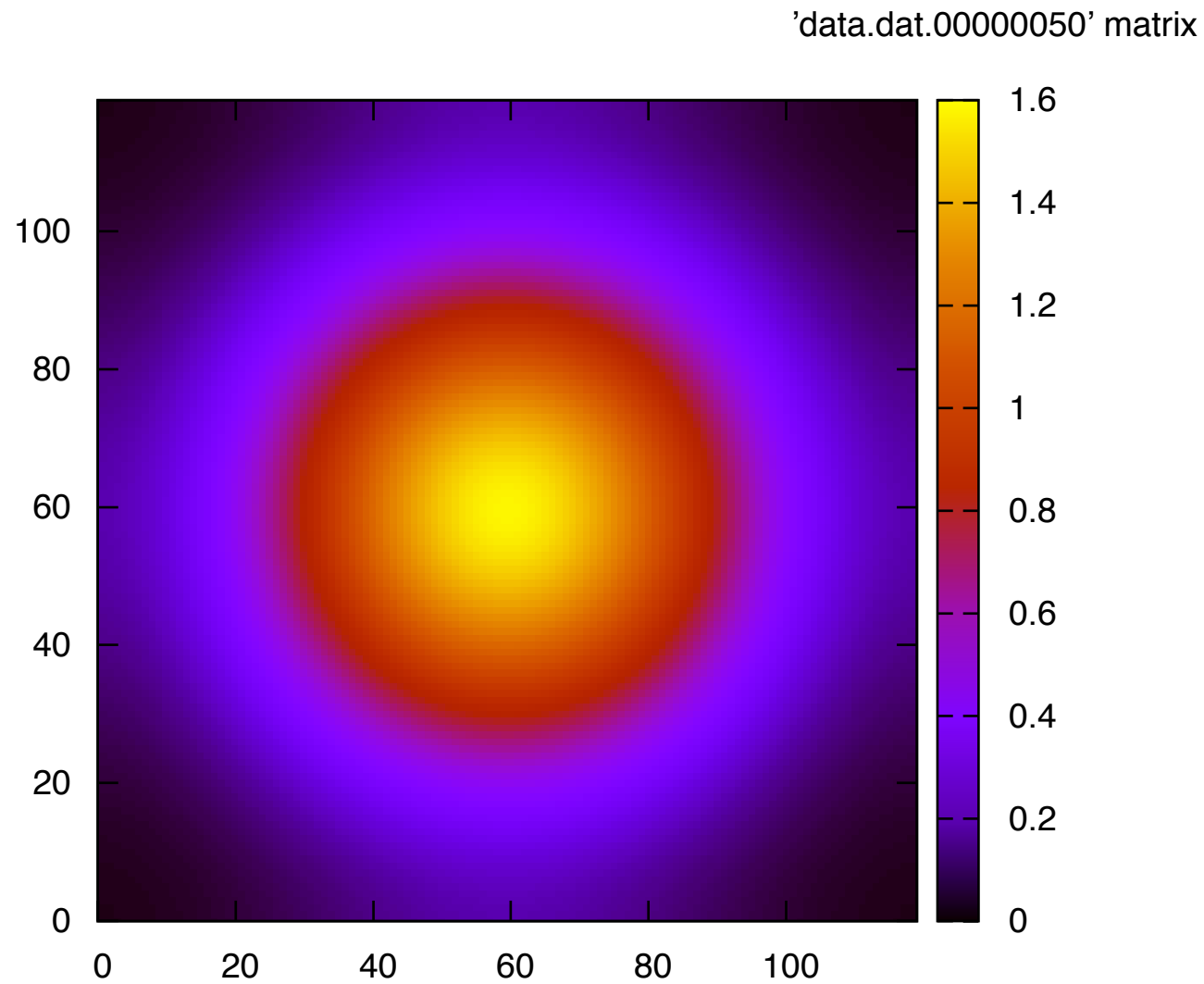
Ex1: DIFFUSION - 2D4 NEIGHBOURHOOD, 15X15











EXAMPLE 2:

TURING PATTERNS

Liu, Blätke, Heiner, Yang:
Modelling and simulating reaction–diffusion systems using coloured Petri nets;
Computers in Biology and Medicine, 53:297–308, October 2014

“How the Leopard Got Its Spots”

❑ **morphogenesis**

- > *developmental pattern formation in bio systems*
- > *the process that controls the organized spatial distribution of cells*
- > *tiger stripes, leopard spots, the precisely spaced rows of alligator teeth, etc.*

❑ **Turing's theory of biological pattern formation, 1952**

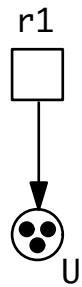
- > *patterns form as result of*
the interactions between two chemicals
that spread throughout a system at different rates

❑ **highly simplified and idealised take on biological patterning**

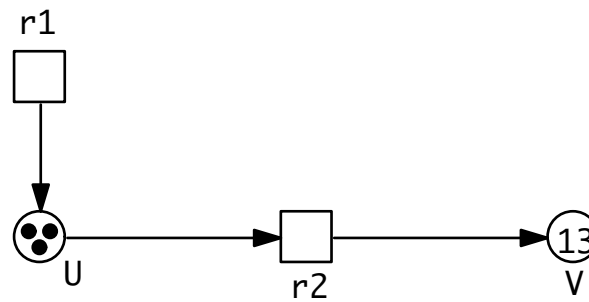
❑ **mathematical challenge**

- > *For which parameters do stable/oscillating Turing patterns exist ?*
- > *analysis of stability, multistability, bifurcation of non-linear PDE*

r1: -> U

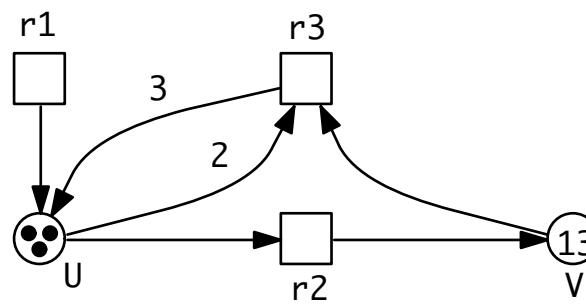


r1: $\rightarrow U$
r2: $U \rightarrow V$

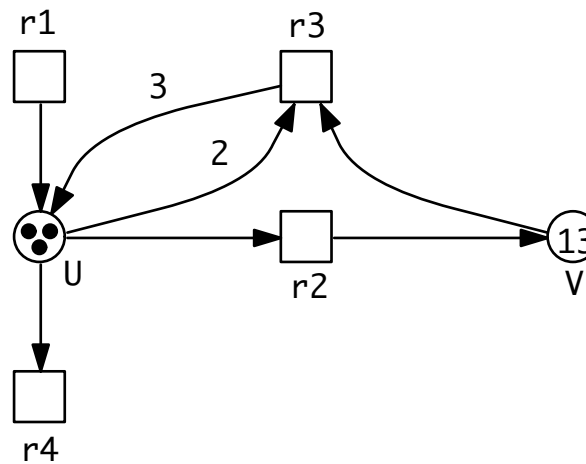


Ex2: TURING PATTERNS

r1: $\rightarrow U$
r2: $U \rightarrow V$
r3: $2U + V \rightarrow 3U$

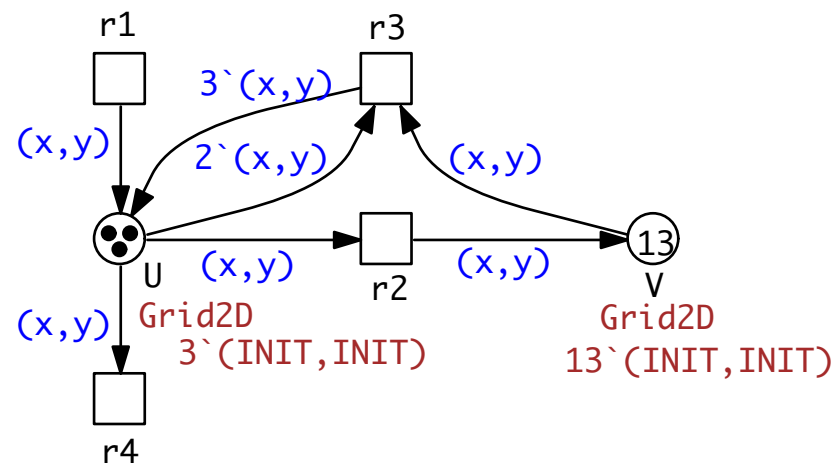


r1: $\rightarrow U$
r2: $U \rightarrow V$
r3: $2U + V \rightarrow 3U$
r4: $U \rightarrow$



r1: $\rightarrow U$
 r2: $U \rightarrow V$
 r3: $2U + V \rightarrow 3U$
 r4: $U \rightarrow$

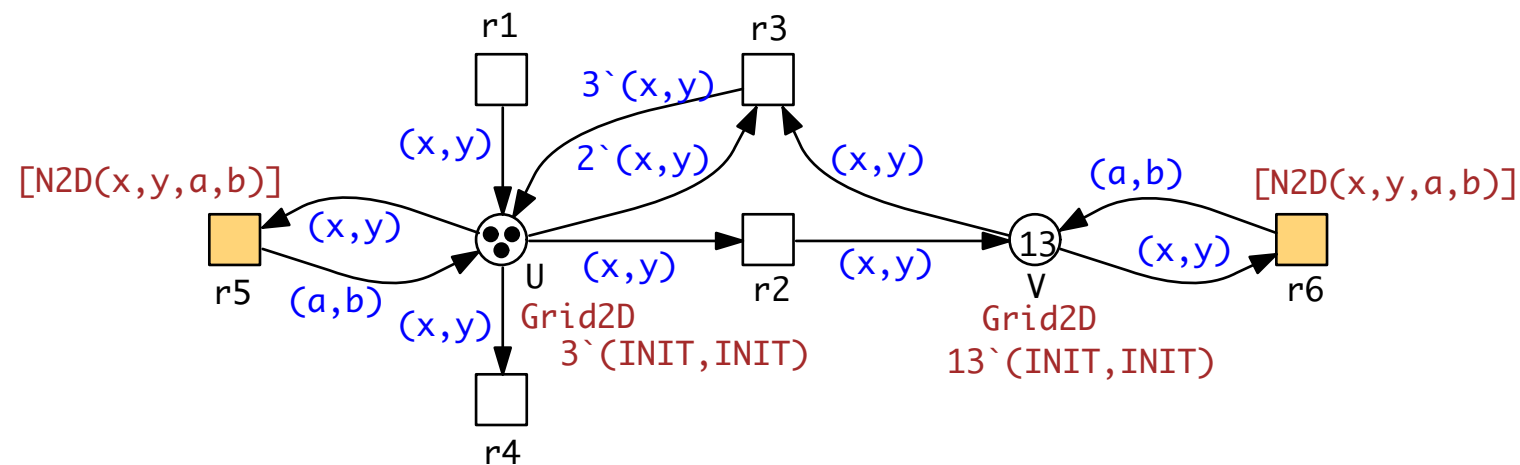
adding SPACE



$r1: \quad \rightarrow U$
 $r2: \quad U \rightarrow V$
 $r3: \quad 2U + V \rightarrow 3U$
 $r4: \quad U \rightarrow$

diffusion:

$r5: \quad U_{xy} \xrightarrow{1/h^2} U_{ab}$
 $r6: \quad V_{xy} \xrightarrow{D/h^2} V_{ab}$



$r1 - r4$ follow mass action kinetics with rate constants:

$r1: A, r2: B, r3: 1, r4: 1;$

❑ reactions

-> *version of Brusselator model, <http://en.wikipedia.org/wiki/Brusselator>*

❑ parameters

-> *Pena, Perez-Garcia: Stability of Turing patterns in the Brusselator model, Physical Review 2001*

-> $A = 4.5$, $B = 0.04 \dots 0.98$, $D = 128$, $h = 0.8$

❑ unfolding

-> *runtime (constraint solver, 4 threads): 128 sec*

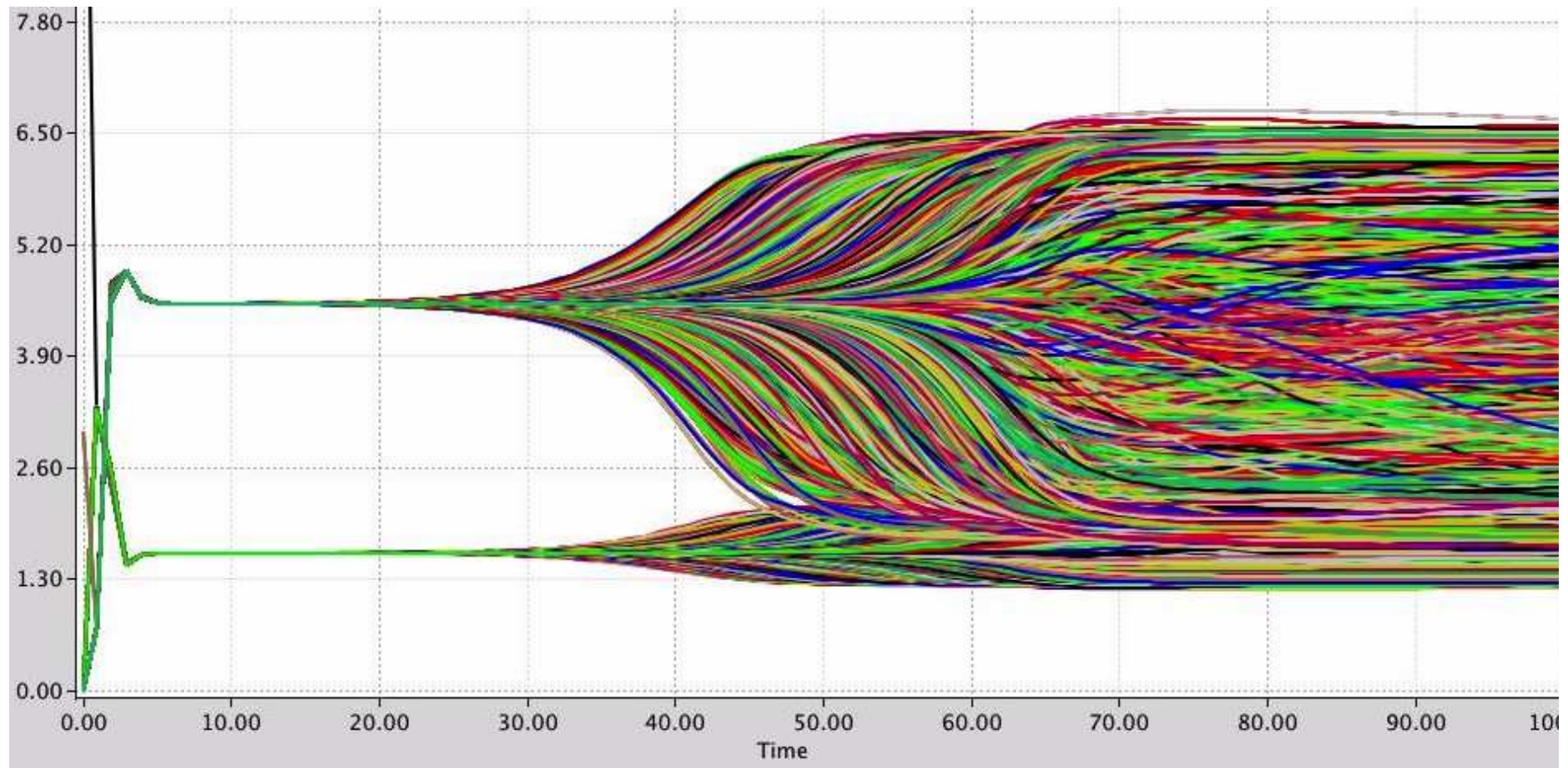
-> *places: 32,768, transitions: 324,616*

❑ continues simulation

-> *BDF (Backward Differentiation Formulae, higher-order stiffly stable solver)*

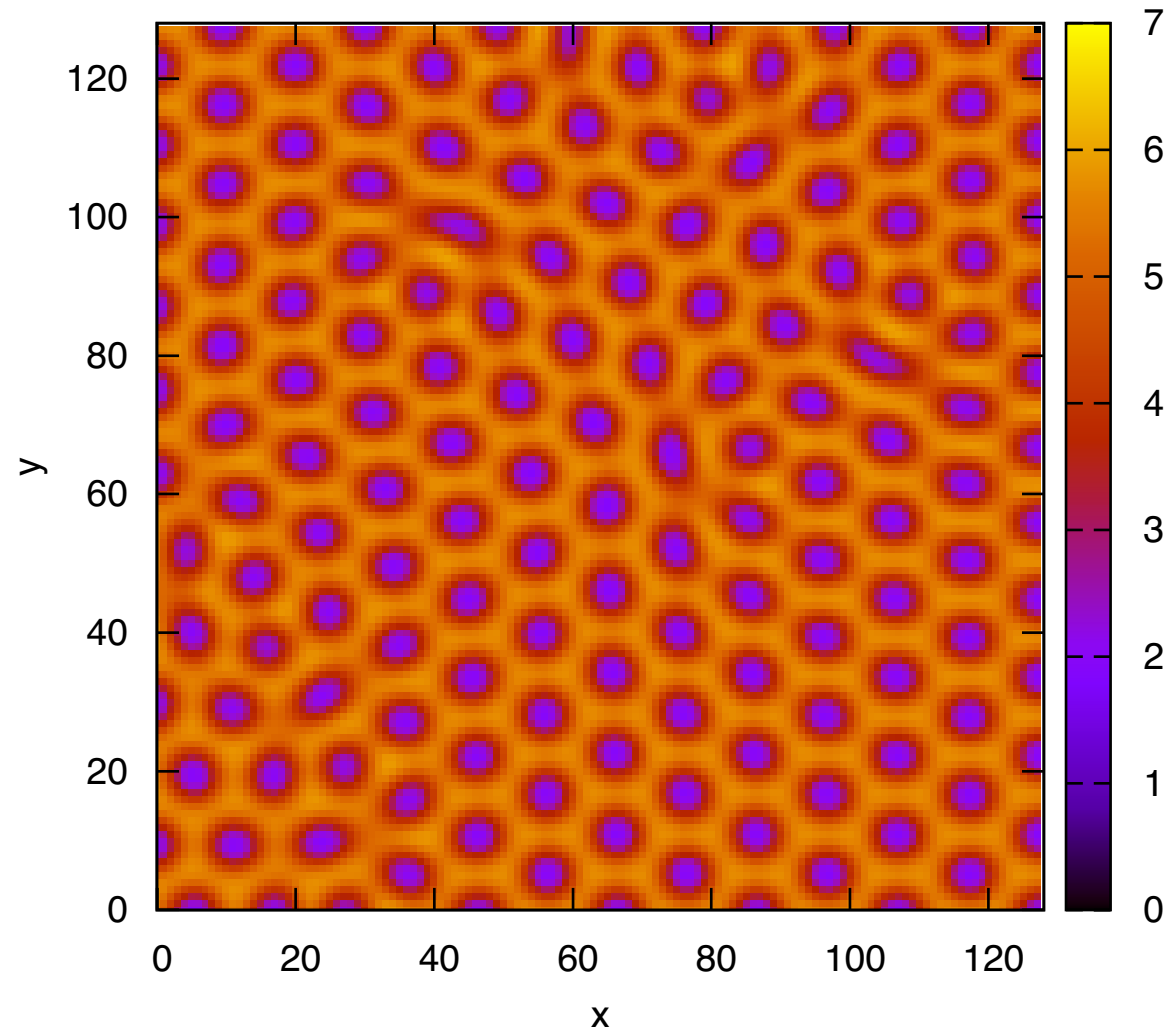
-> *simulation time: 5,000 -> runtime: about 30h*

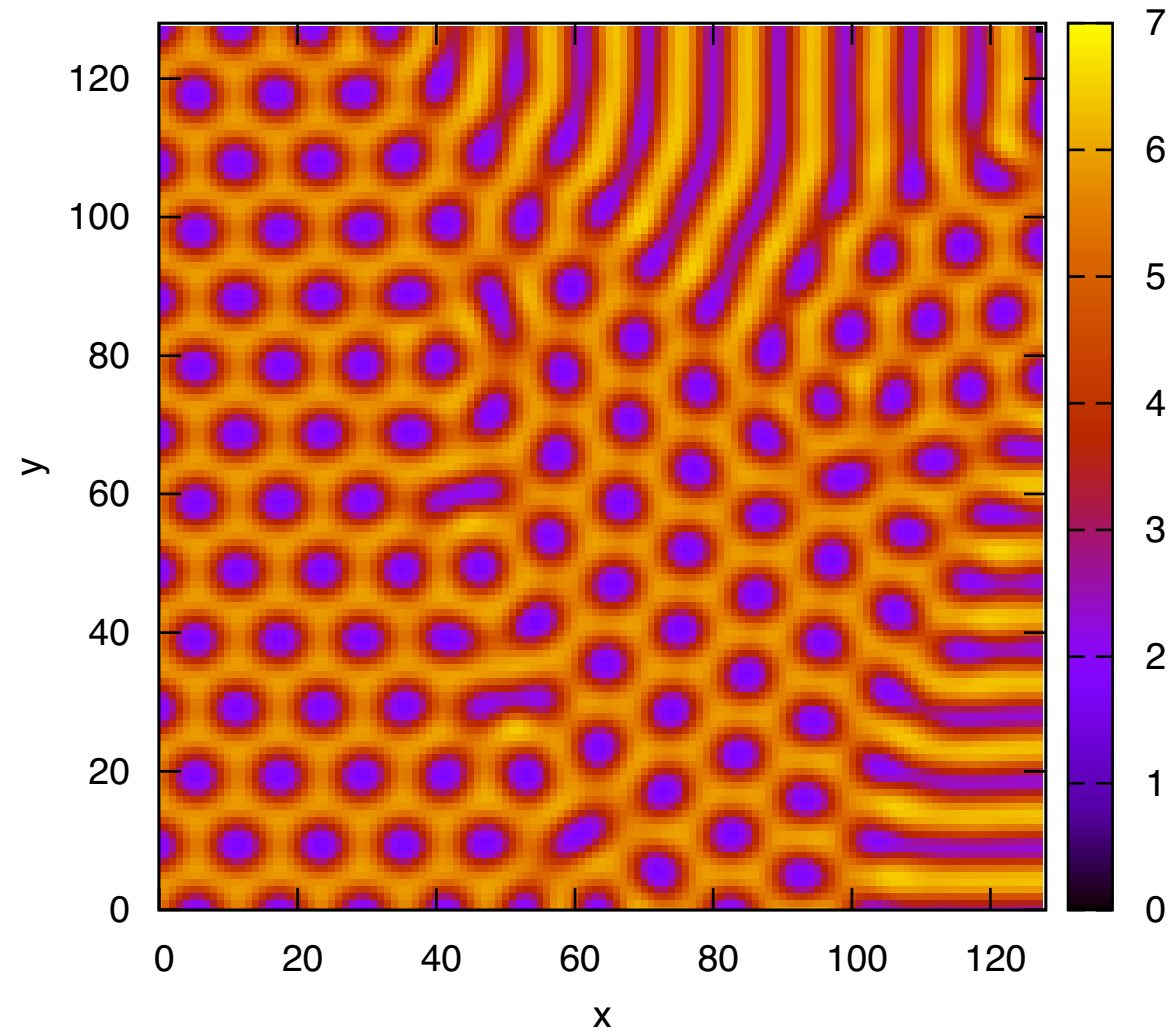
-> EVOLUTION OF U, V IN ALL GRID POSITIONS OVER TIME

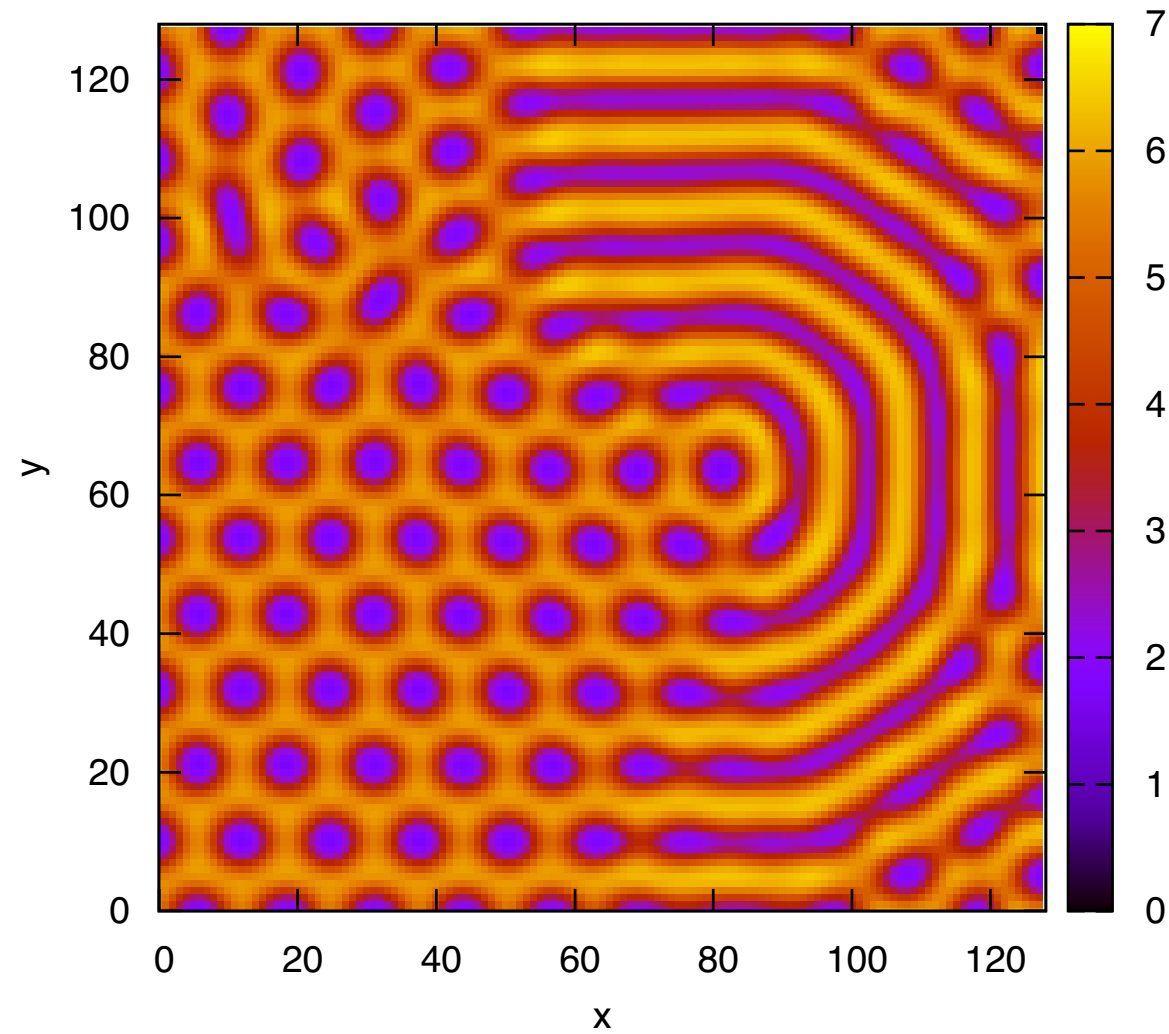


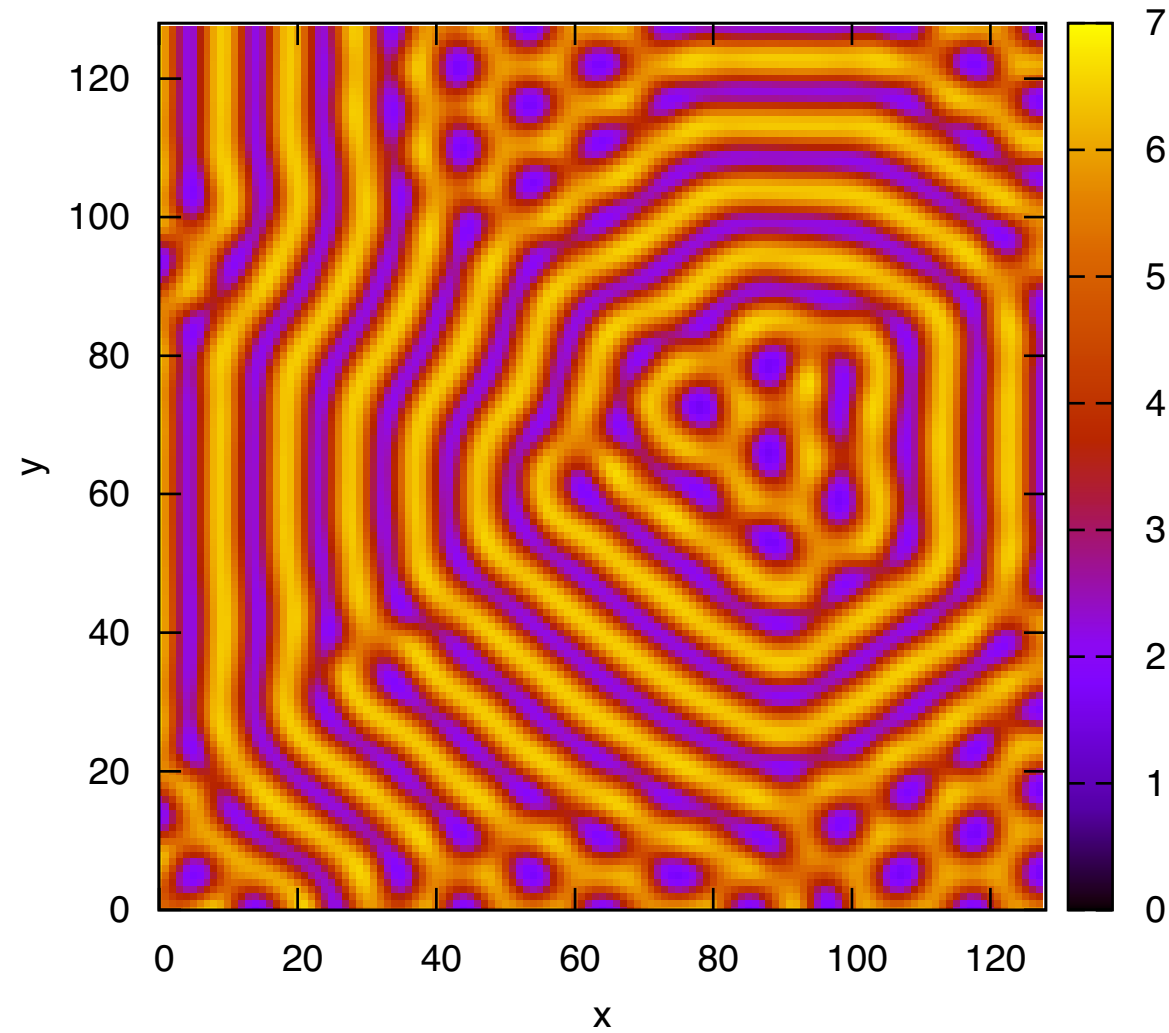
Ex2: TURING PATTERNS

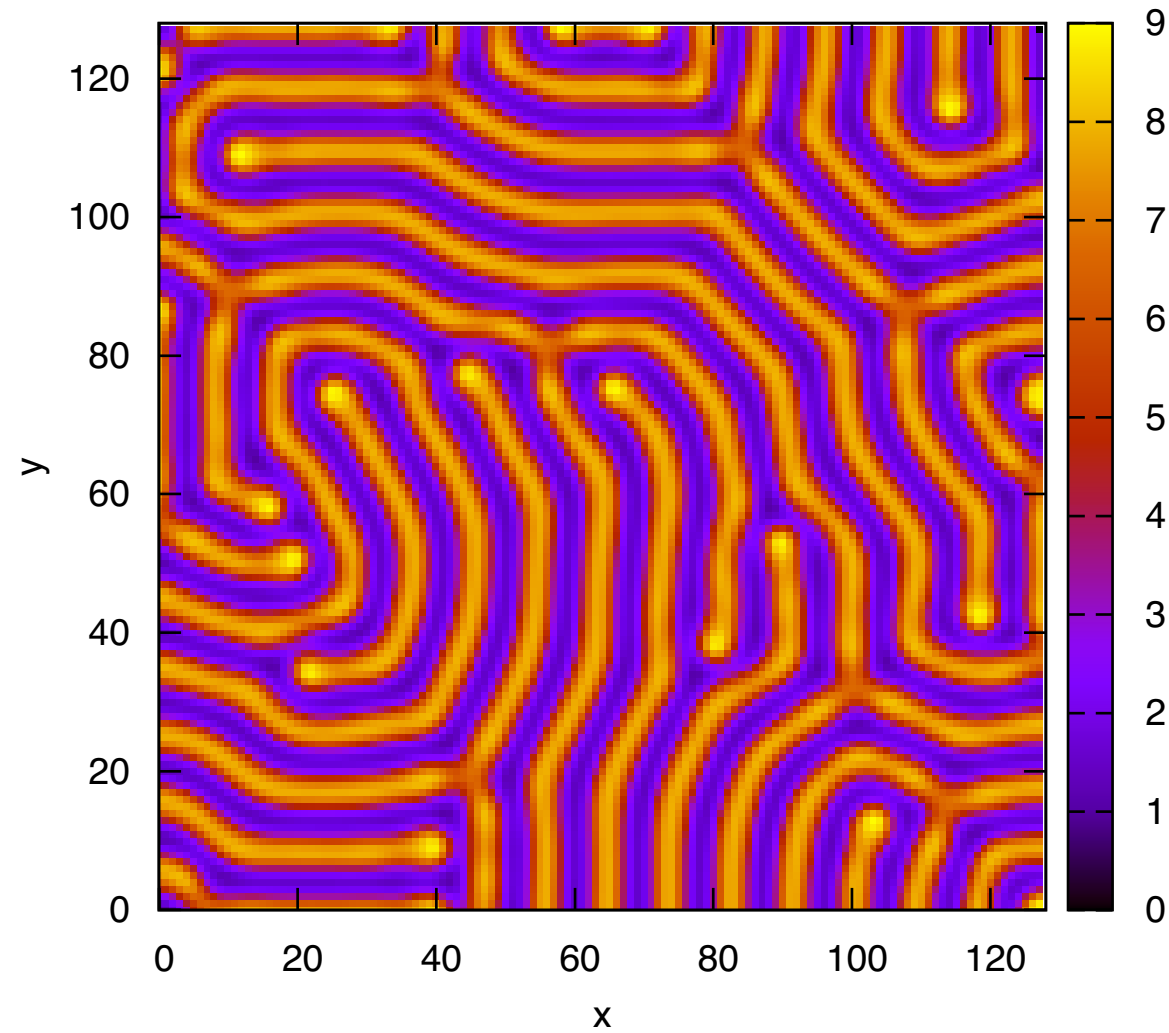
-> U IN ALL GRID POSITIONS AT TIME 5,000

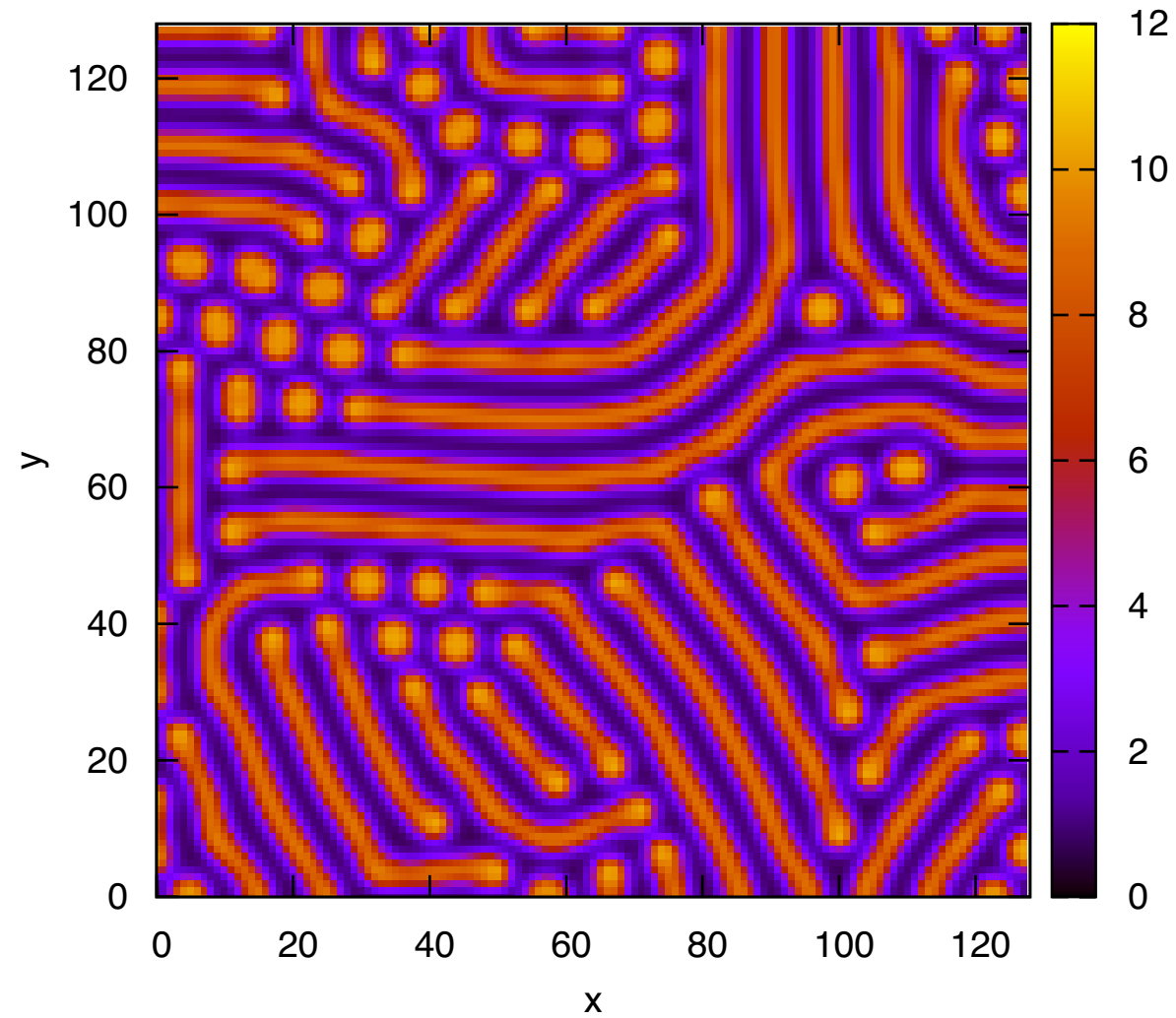


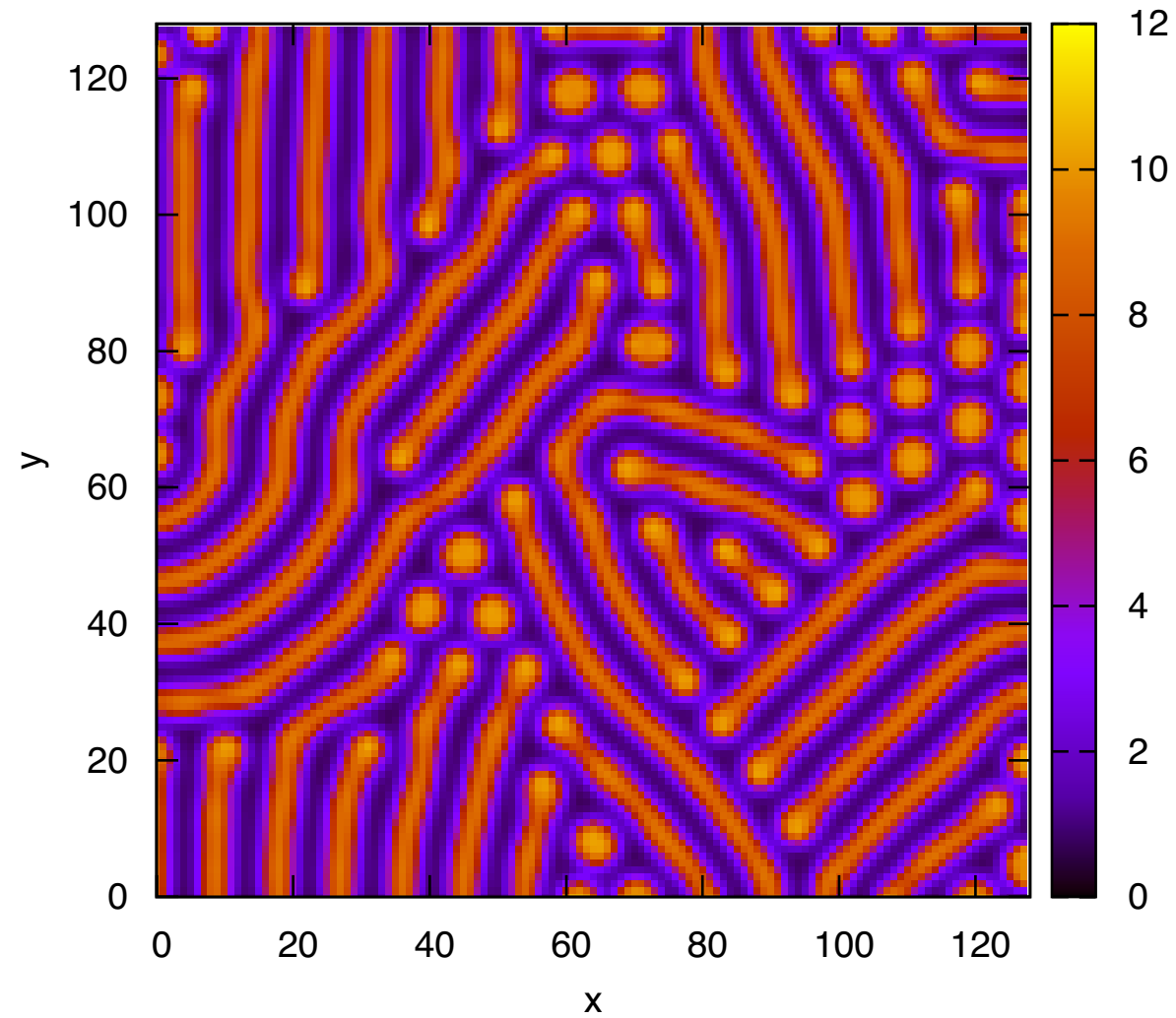


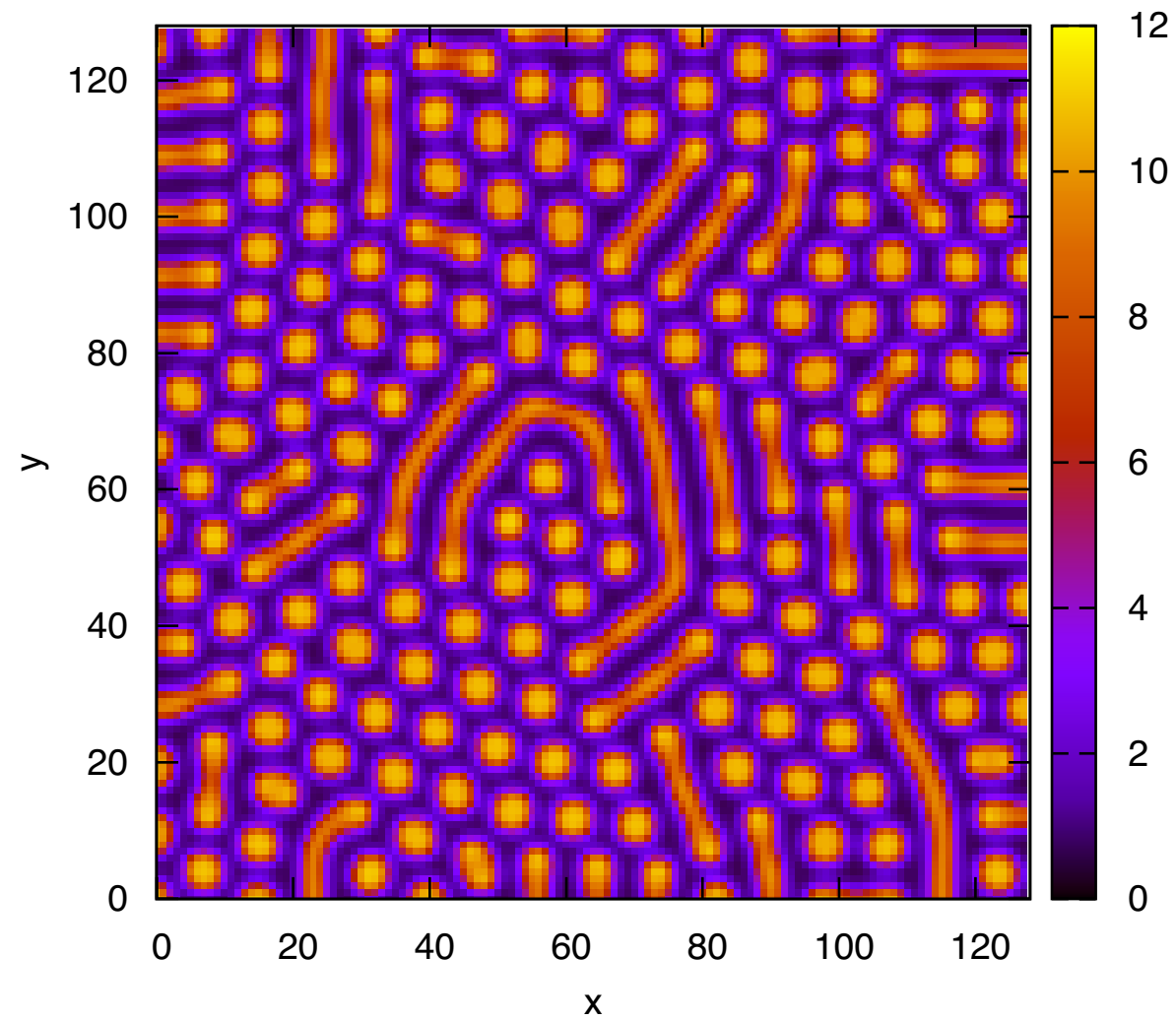


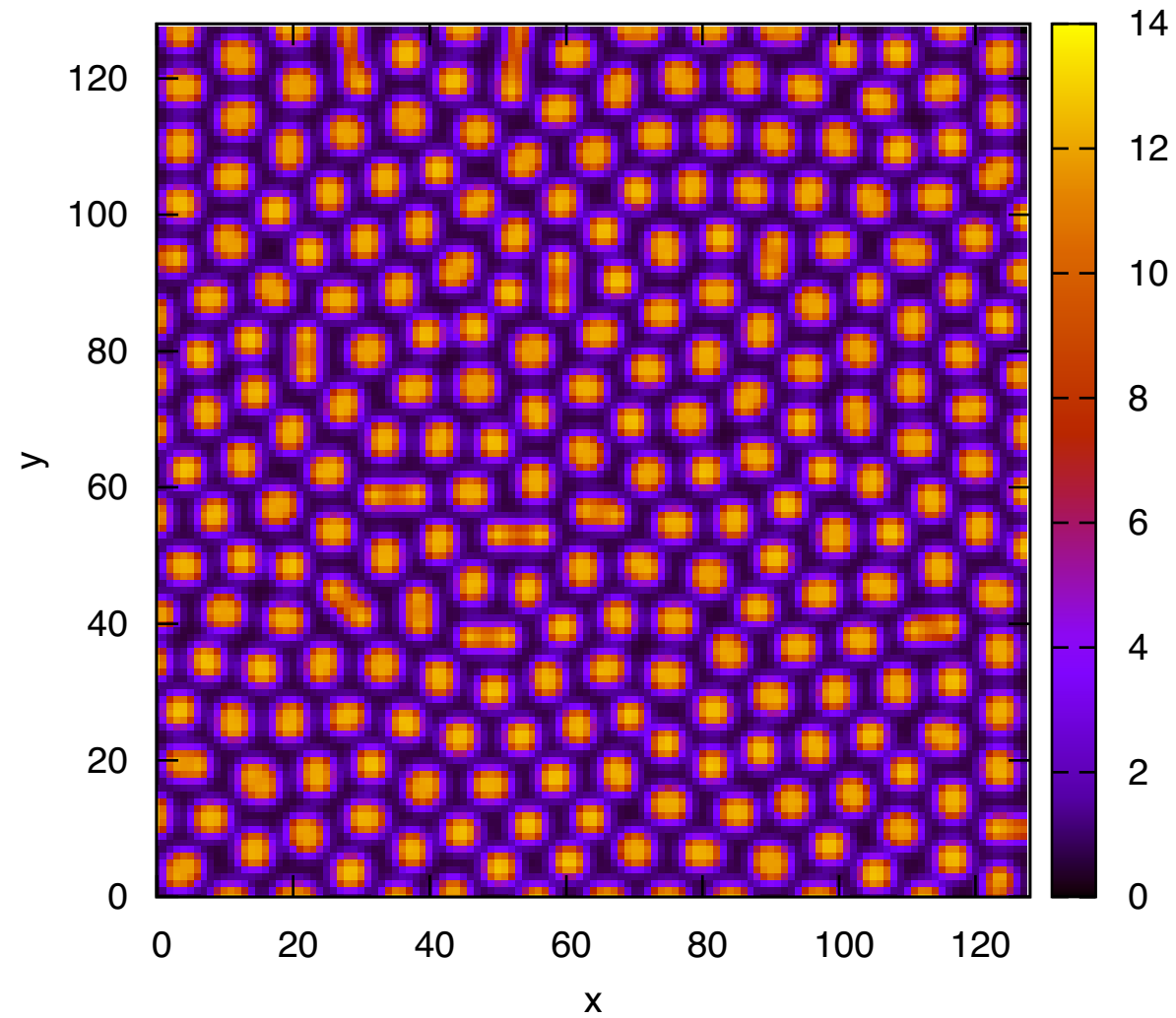












EXAMPLE 3:

PHASE VARIATION IN MULTISTRAIN CELL COLONIES

Pârvu, Gilbert, Heiner, Liu, Saunders, Shaw:
Spatial-temporal modelling and analysis of bacterial colonies with phase variable genes;
ACM TOMACS, 25(2):25p., May 2015.

❑ phase variation

-> *method for dealing with rapidly varying environments without requiring random mutations*

❑ contingency genes

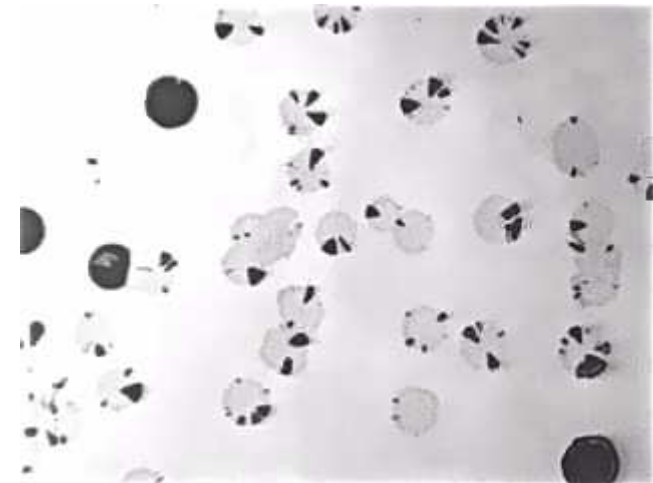
-> *populations include variants adapted to “foreseeable” frequently encountered environmental or selective conditions*

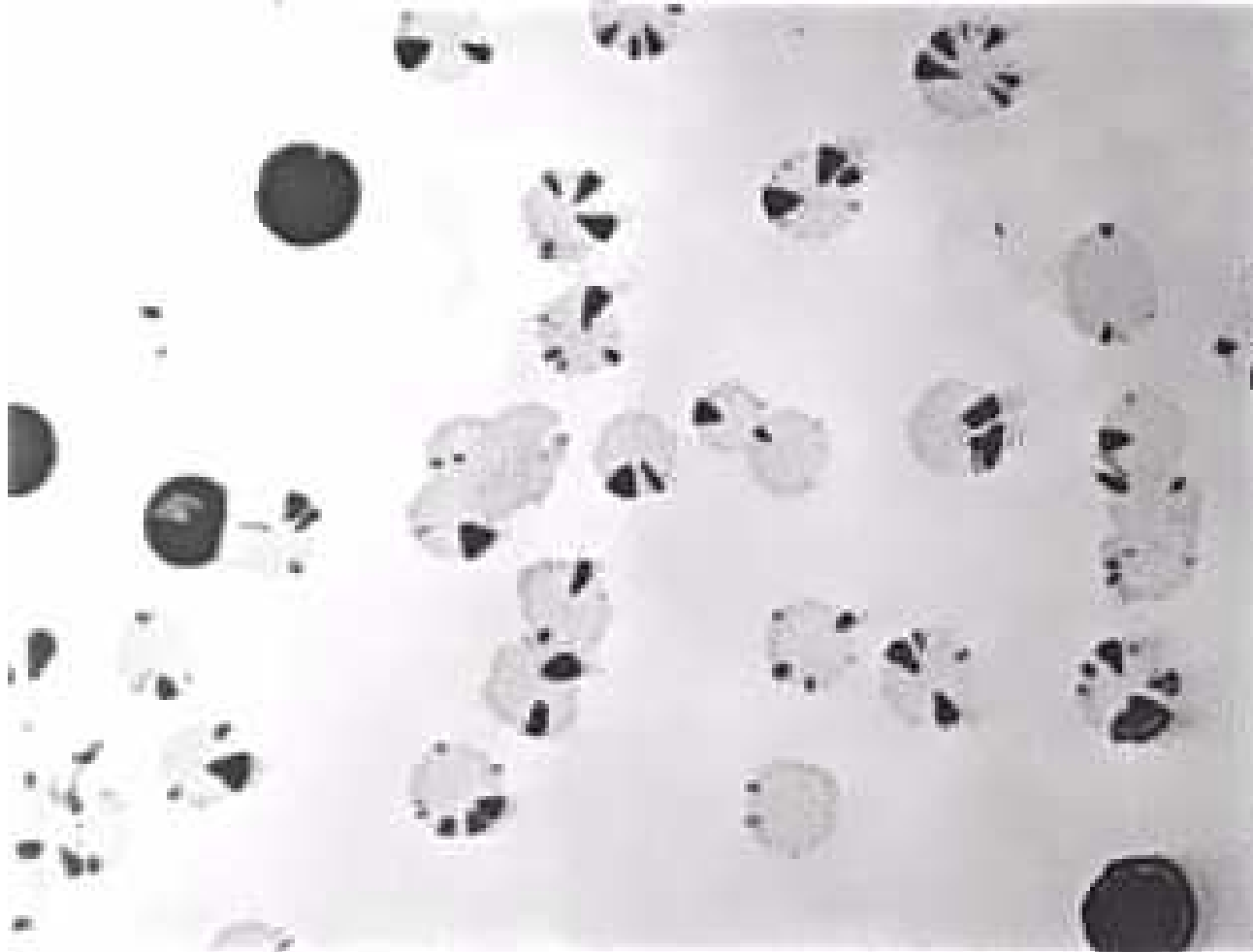
❑ stochastic gene switching process

-> *controlled by reversible gene mutations, inversions, or epigenetic modification*
-> *e.g. switch between two phenotypes A, B*

❑ colonial sectoring

-> *observable effect in cultures grown in vitro*





(courtesy of N Saunders)

Microbiology (2003), **149**, 485–495

DOI 10.1099/mic.0.25807-0

Mutation rates: estimating phase variation rates when fitness differences are present and their impact on population structure

Nigel J. Saunders,^{1†} E. Richard Moxon¹ and Mike B. Gravenor²

Correspondence

Nigel J. Saunders
saunders@molbiol.ox.ac.uk

¹Molecular Infectious Diseases Group, Institute of Molecular Medicine, University of Oxford, Headington, Oxford OX3 9DS, UK

²Institute for Animal Health, Compton, Berkshire RG20 7NN, UK

Phase variation is a mechanism of ON–OFF switching that is widely utilized by bacterial pathogens. There is currently no standardization to how the rate of phase variation is determined experimentally.

Microbiology (2003), **149**, 485–495

DOI 10.1093/mic/0.25807-0

Mutation rates: estimating phase variation rates when fitness differences are present and their impact on population structure

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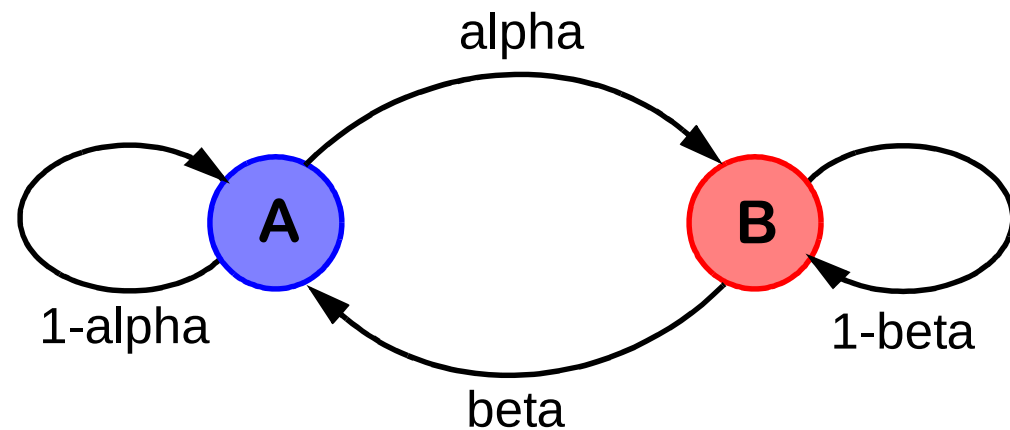
Phase variation is a mechanism of ON–OFF switching that is widely utilized by bacterial pathogens. There is currently no standardization to how the rate of phase variation is determined experimentally.

❑ two cell types: phenotype A and B

❑ cell divide

-> *cell division may involve mutation of the offspring*

-> *parent cell keeps its phenotype*



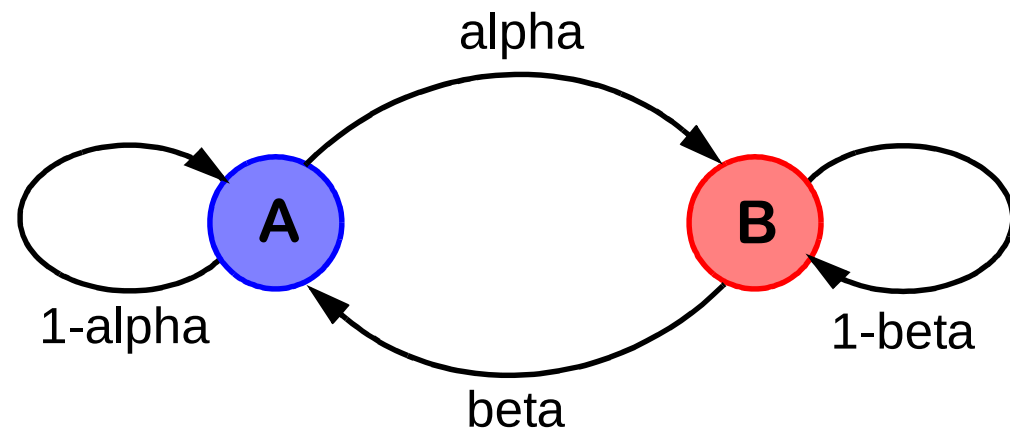
❑ two cell types: phenotype A and B

❑ cell divide

- > cell division may involve mutation of the offspring
- > parent cell keeps its phenotype

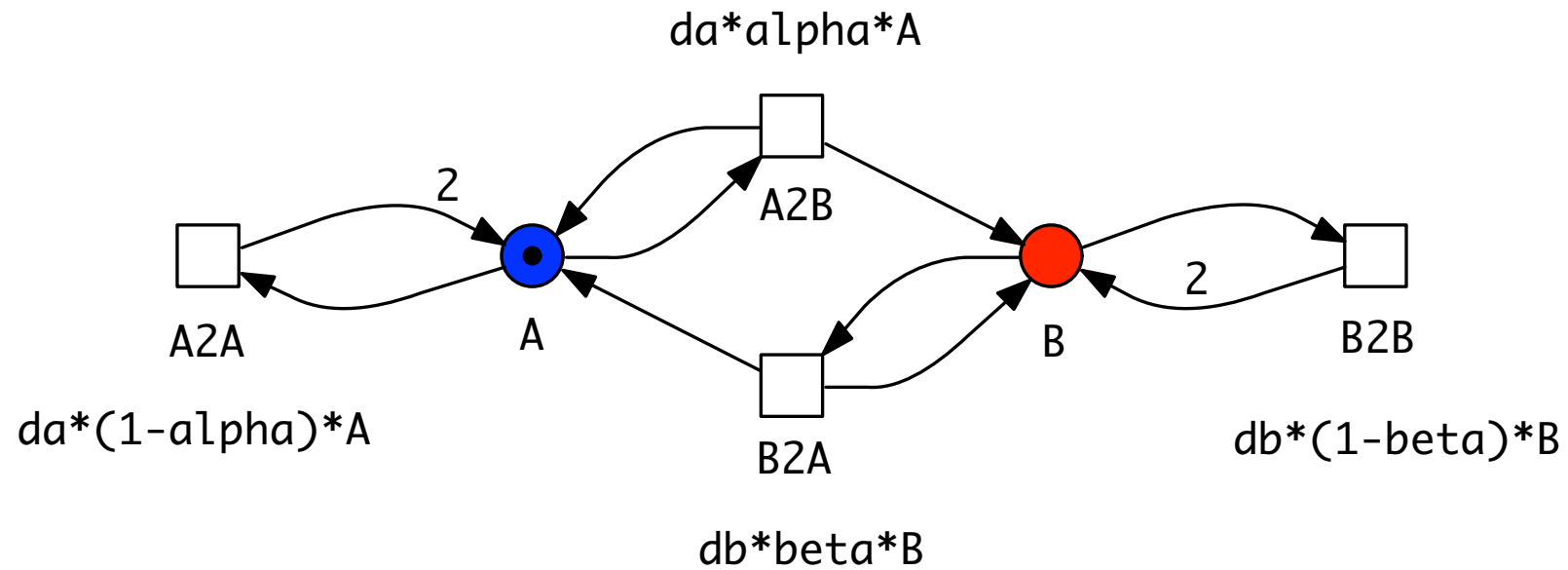
❑ model parameters

- > $\alpha = \beta$ - mutation rates
- > d_A, d_B - fitness of A, B
- > d_A/d_B - relative fitness

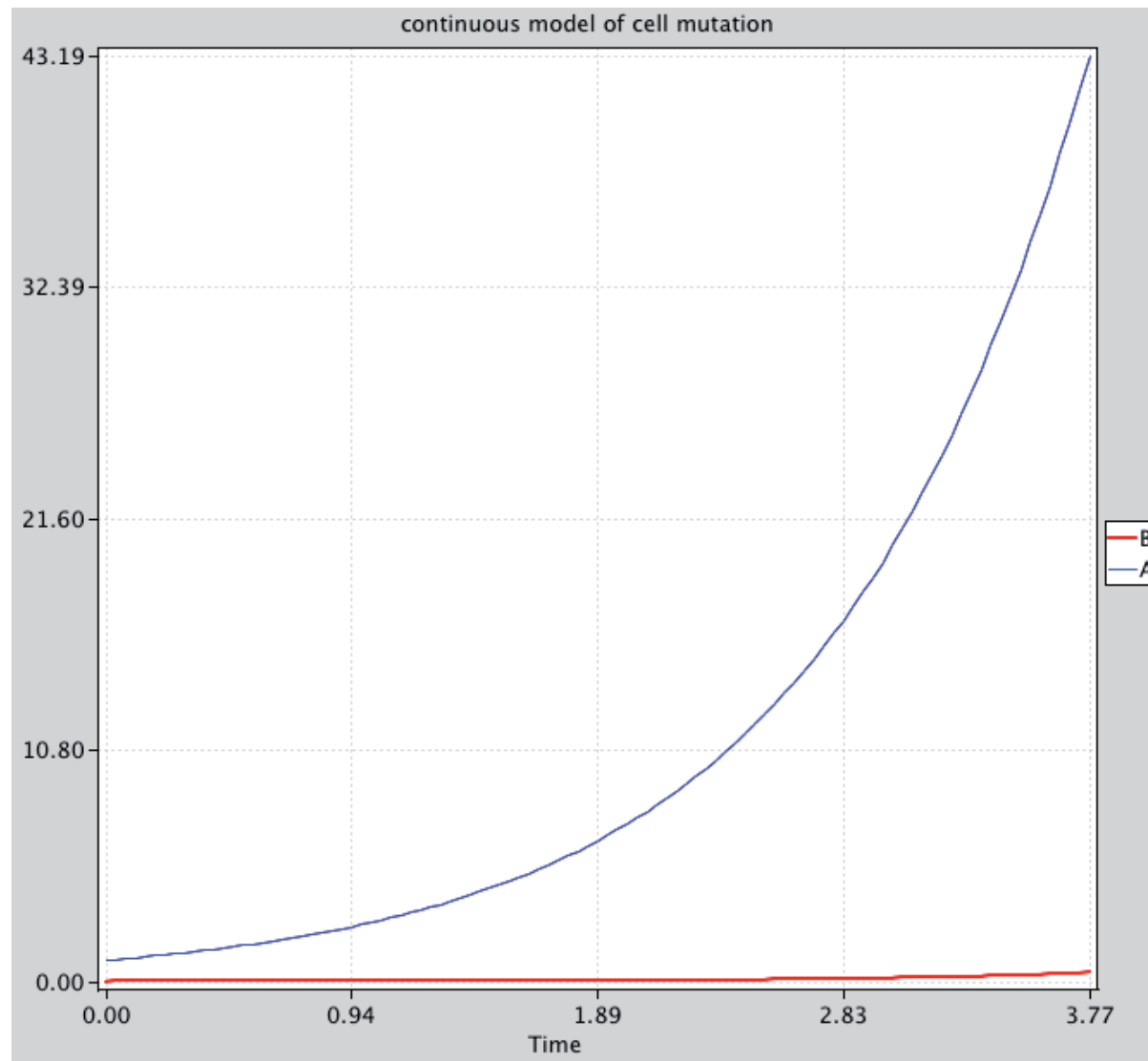


❑ output

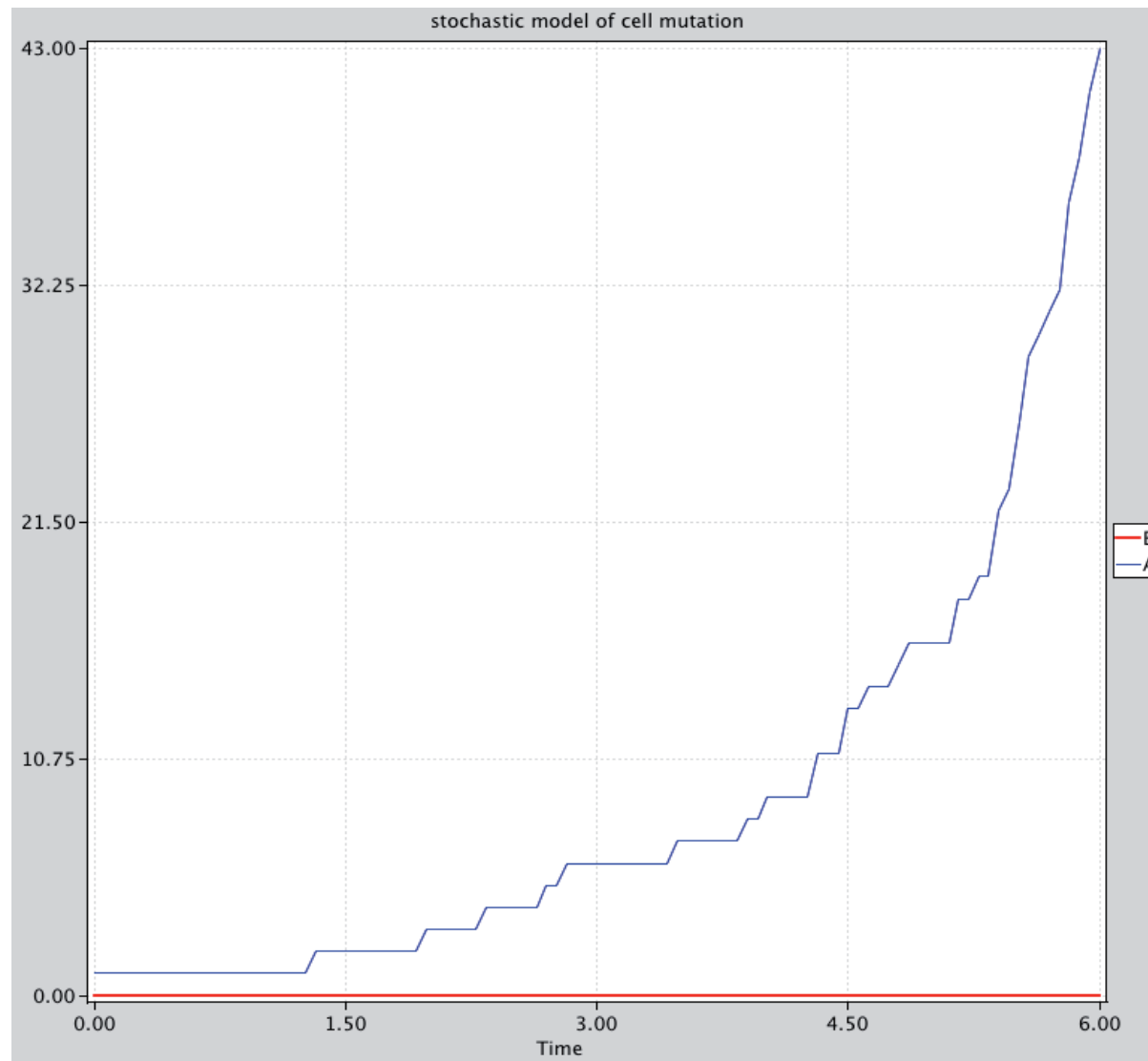
- > total number of cells
- > proportion of A = $A / (A + B)$
- > proportion of B = $B / (A + B)$



Ex3: CELL COLONIES, CONTINUOUS PLOT



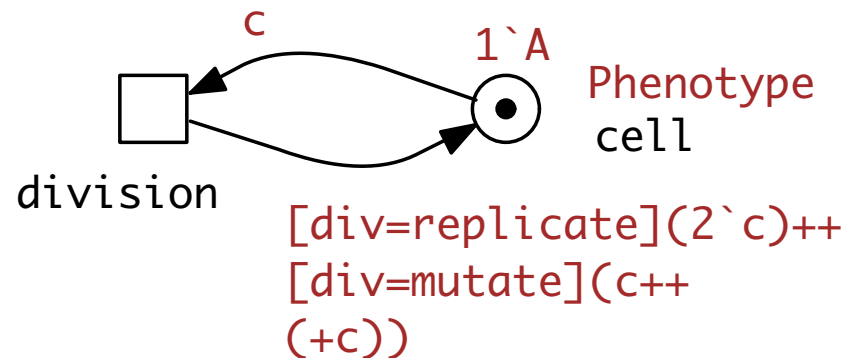
Ex3: CELL COLONIES, STOCHASTIC PLOT



```
colorset Phenotype    = enum with A, B;  
colorset DivisionType = enum with replicate , mutate ;
```

colorset Phenotype = **enum with** A, B;

colorset DivisionType = **enum with** replicate , mutate ;



```
(c=A) & (div=replicate) : cell*da*(1-alpha)  
(c=A) & (div=mutate) : cell*(da*alpha)  
(c=B) & (div=replicate) : cell*(db*(1-beta))  
(c=B) & (div=mutate) : cell*(db*beta)
```

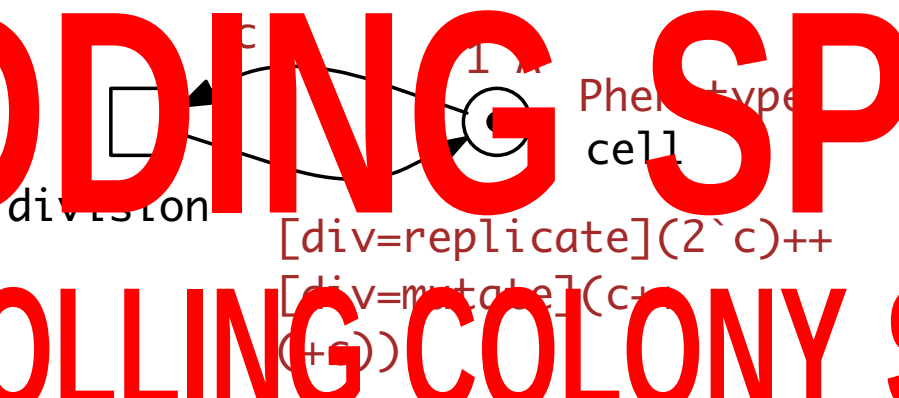
ADDING SPACE

```
(c=A) & (div=replicate) : cell*da*(1-alpha)
(c=A) & (div=mutate) : cell*(da*alpha)
(c=B) & (div=replicate) : cell*(db*(1-beta))
(c=B) & (div=mutate) : cell*(db*beta)
```

colorset Phenotype = **enum with** A, B;
colorset DivisionType = **enum with** replicate , mutate ;

ADDING SPACE

CONTROLLING COLONY SPREADING



```
(c=A) & (div=replicate) : cell*da*(1-alpha)
(c=A) & (div=mutate) : cell*(da*alpha)
(c=B) & (div=replicate) : cell*(db*(1-beta))
(c=B) & (div=mutate) : cell*(db*beta)
```

```
colorset Phenotype = enum with A, B;
colorset DivisionType = enum with replicate, mutate;
```

ADDING SPACE

CONTROLLING COLONY SPREADING

CONTROLLING THICKNESS



```
[div=replicate](2`c)++
[div=mutate](c+
(+c))
(c=A) & (div=replicate) : cell*(da*(1-alpha))
(c=A) & (div=mutate) : cell*(da*alpha)
(c=B) & (div=replicate) : cell*(db*(1-beta))
(c=B) & (div=mutate) : cell*(db*beta)
```

colorset Phenotype = **enum with** A, B;

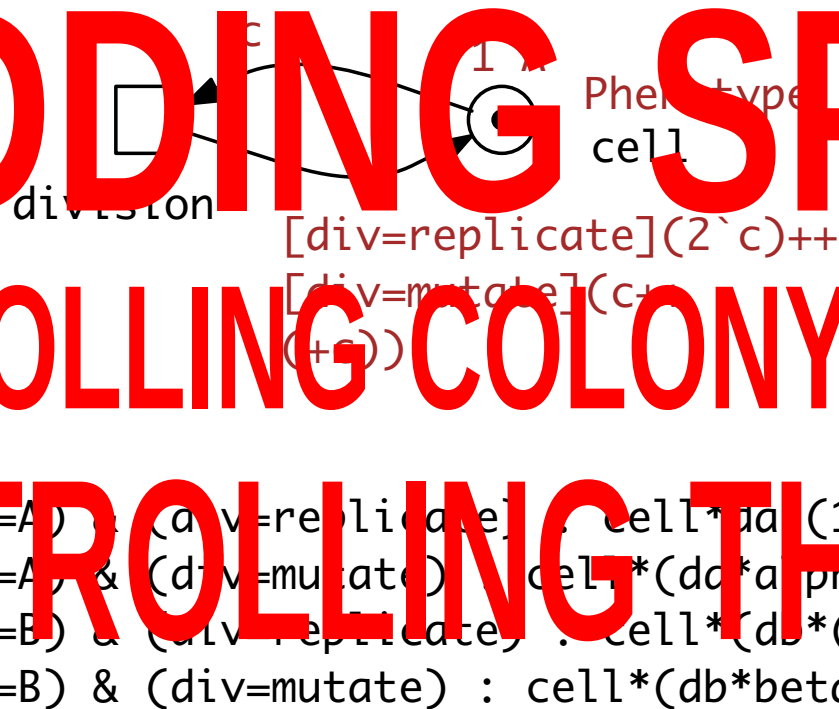
colorset DivisionType = **enum with** replicate , mutate ;

ADDING SPACE

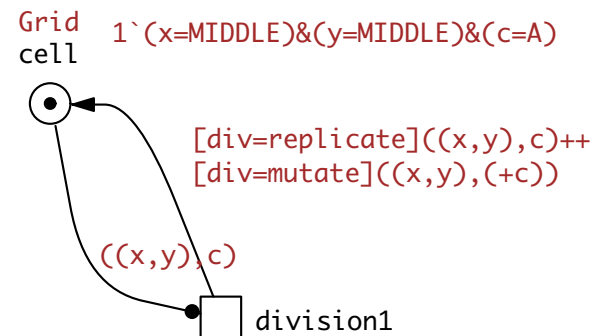
CONTROLLING COLONY SPREADING

CONTROLLING THICKNESS

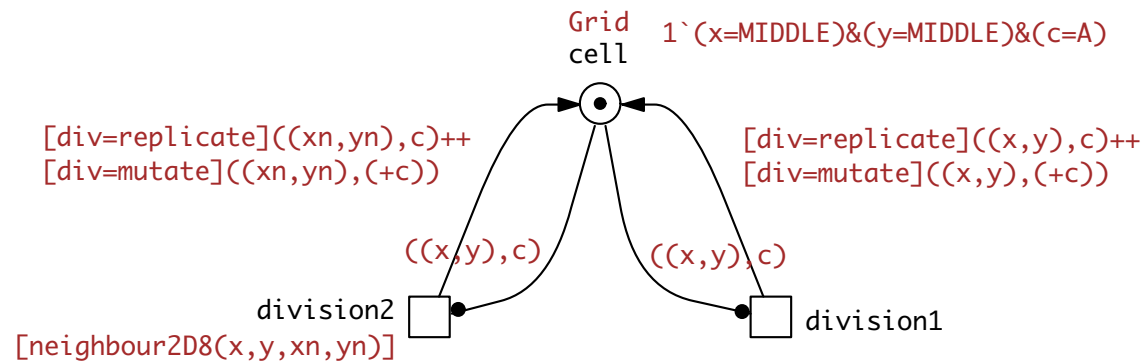
CONTROLLING COLONY SIZE



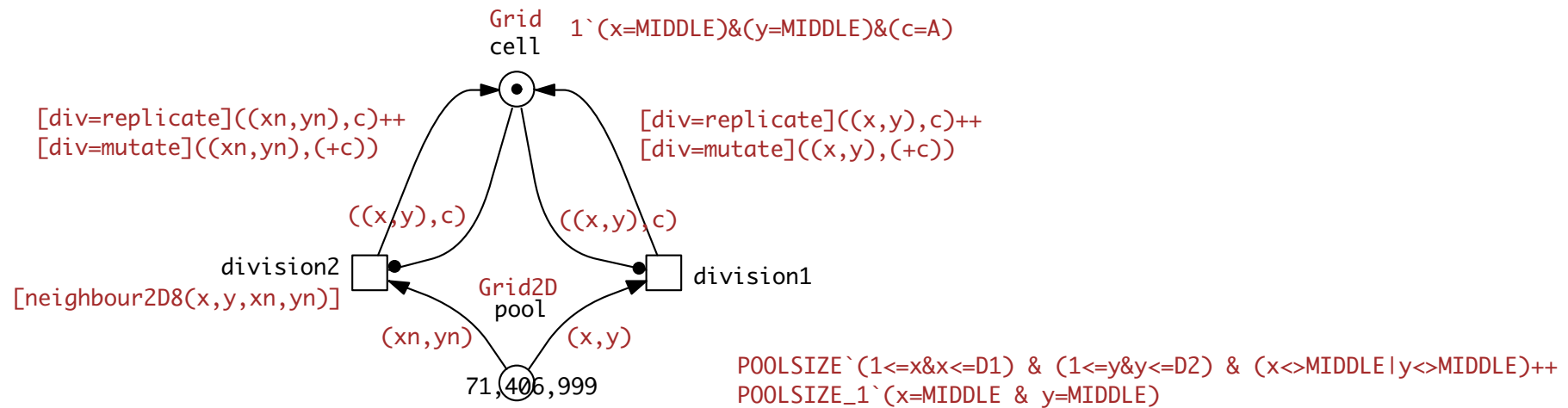
colorset Grid = **product with** Grid2D x Phenotype;



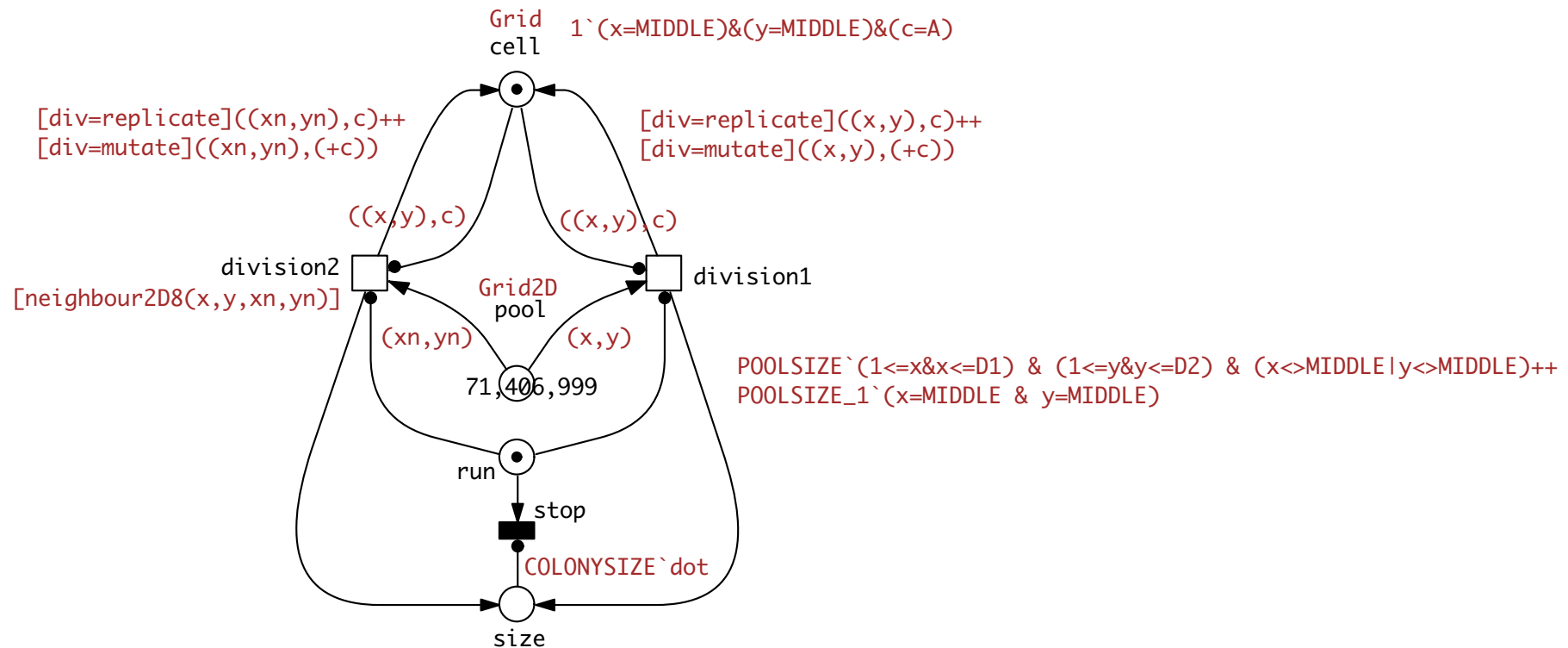
colorset Grid = product with Grid2D x Phenotype;



colorset Grid = product with Grid2D x Phenotype;



colorset Grid = product with Grid2D x Phenotype;



❑ model assumptions

- > *"If phase variation occurs, the progeny consists of one A and one B"*
(Saunders 2003)
- > *It is always the mutant who goes to a neighbouring position, if any.*
- > *constant biofilm thickness (so far)*

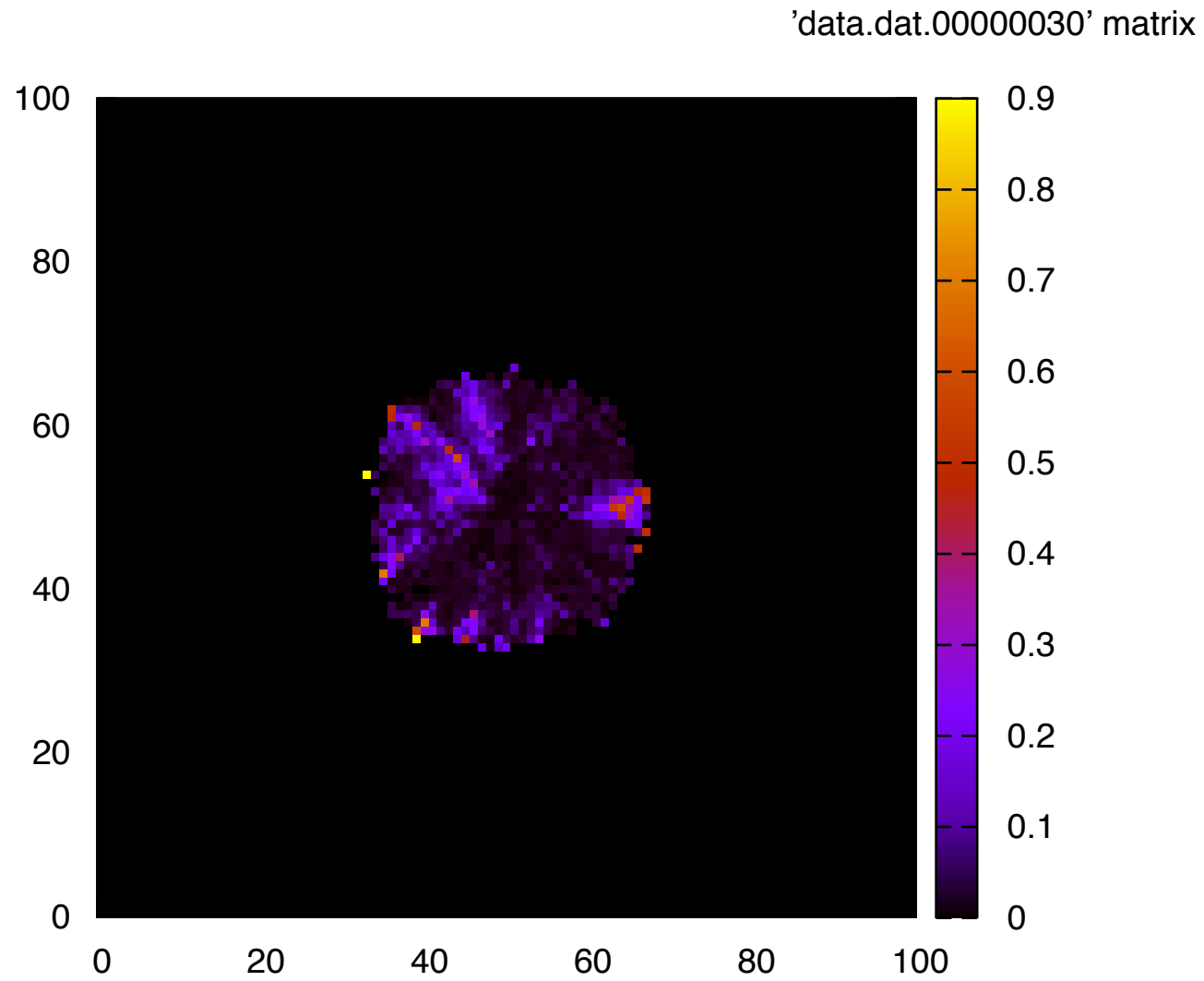
❑ colony size - 24 h

- > 25 generations: 33.5 E+06
- > 26 generations: 67 E+06
- > COLONYSIZE = 70,000,000

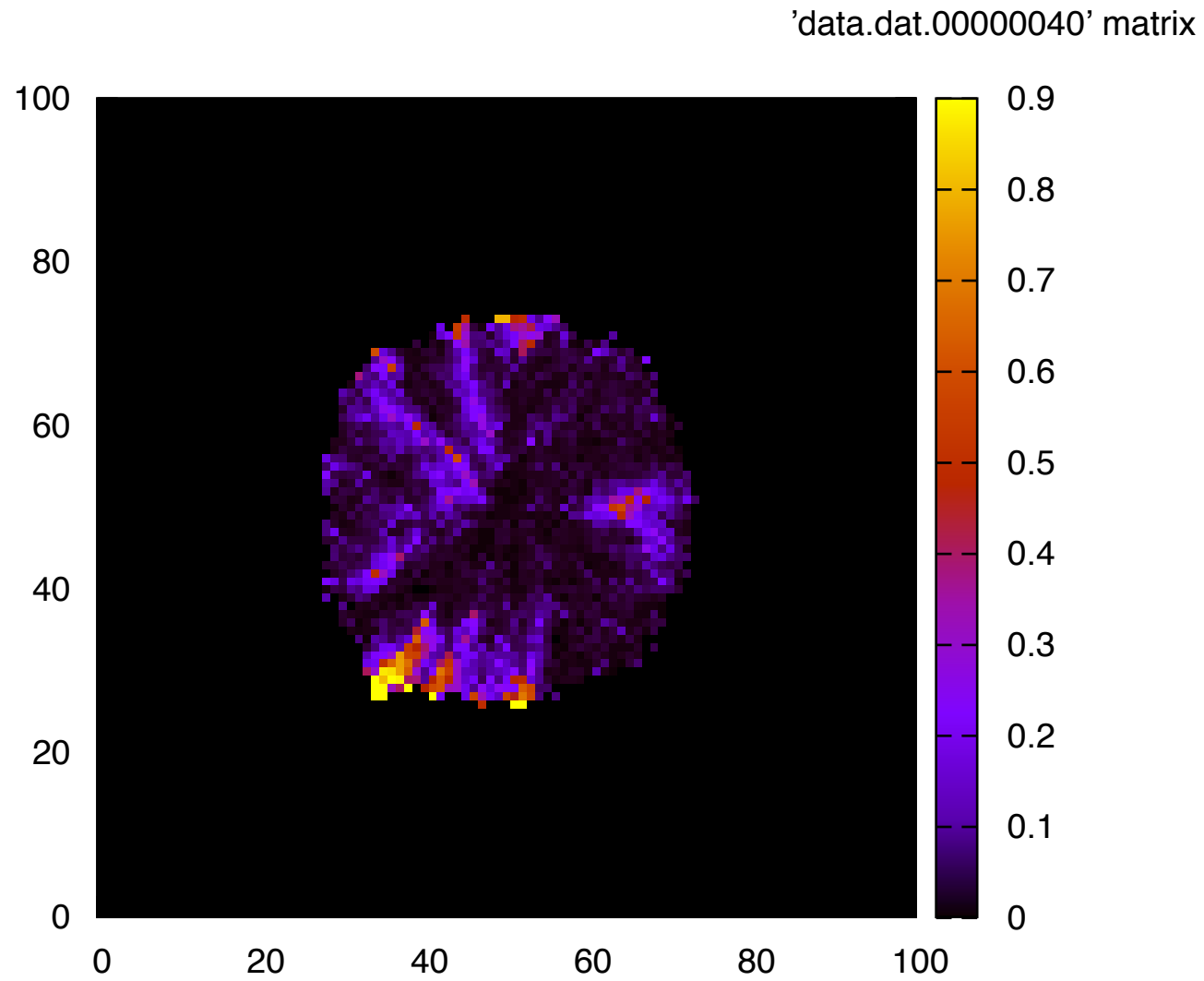
❑ grid size

- > 61 x 61 grid: 11,163 P / 131,044 T; unfolding: 152 sec;
- > 101 x 101 grid: 30,603 P / 362,404 T; unfolding: 9 min;
- > runtime 1 stoch. simulation: 35-40 minutes

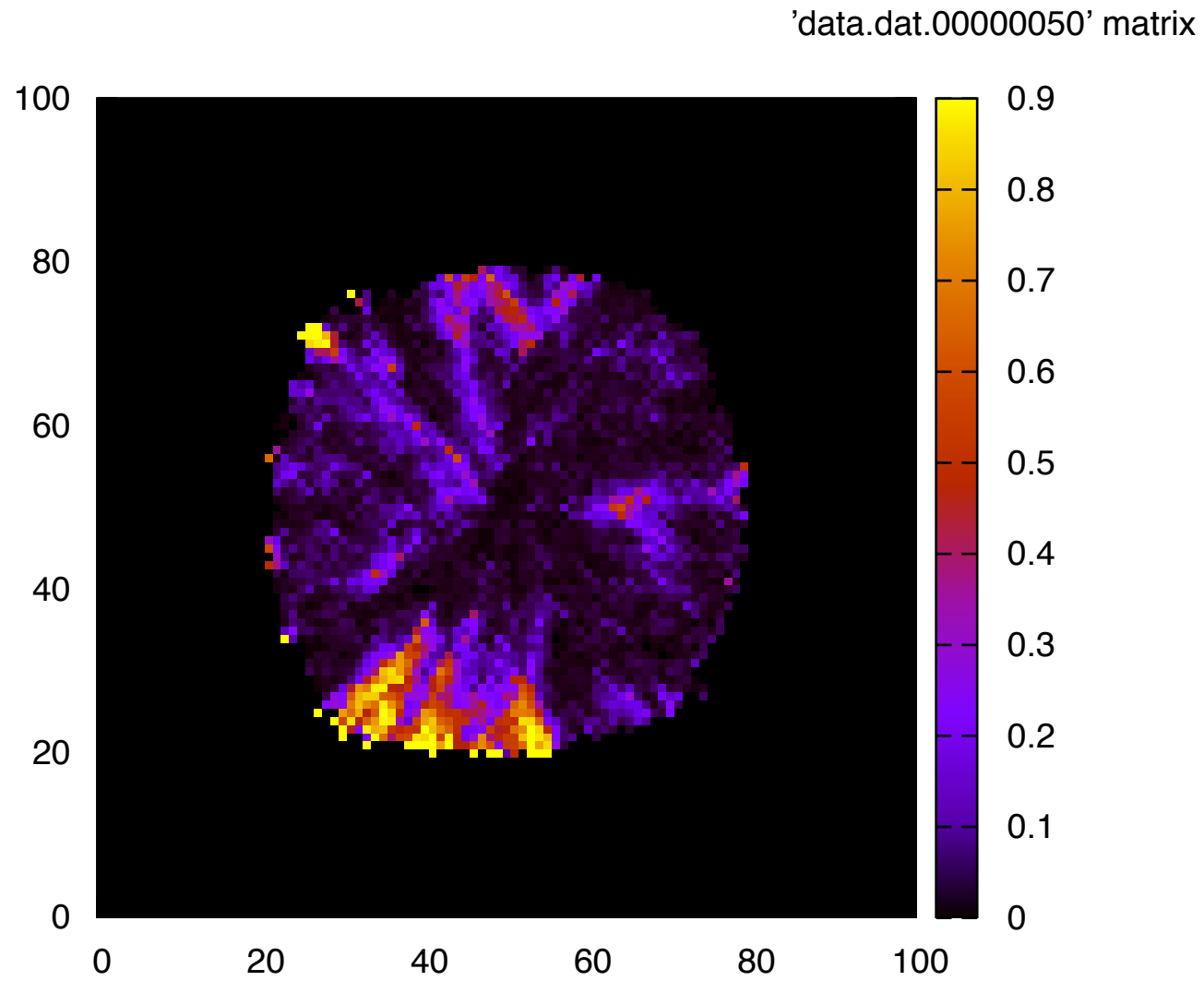
. . . SOME EXPERIMENTS



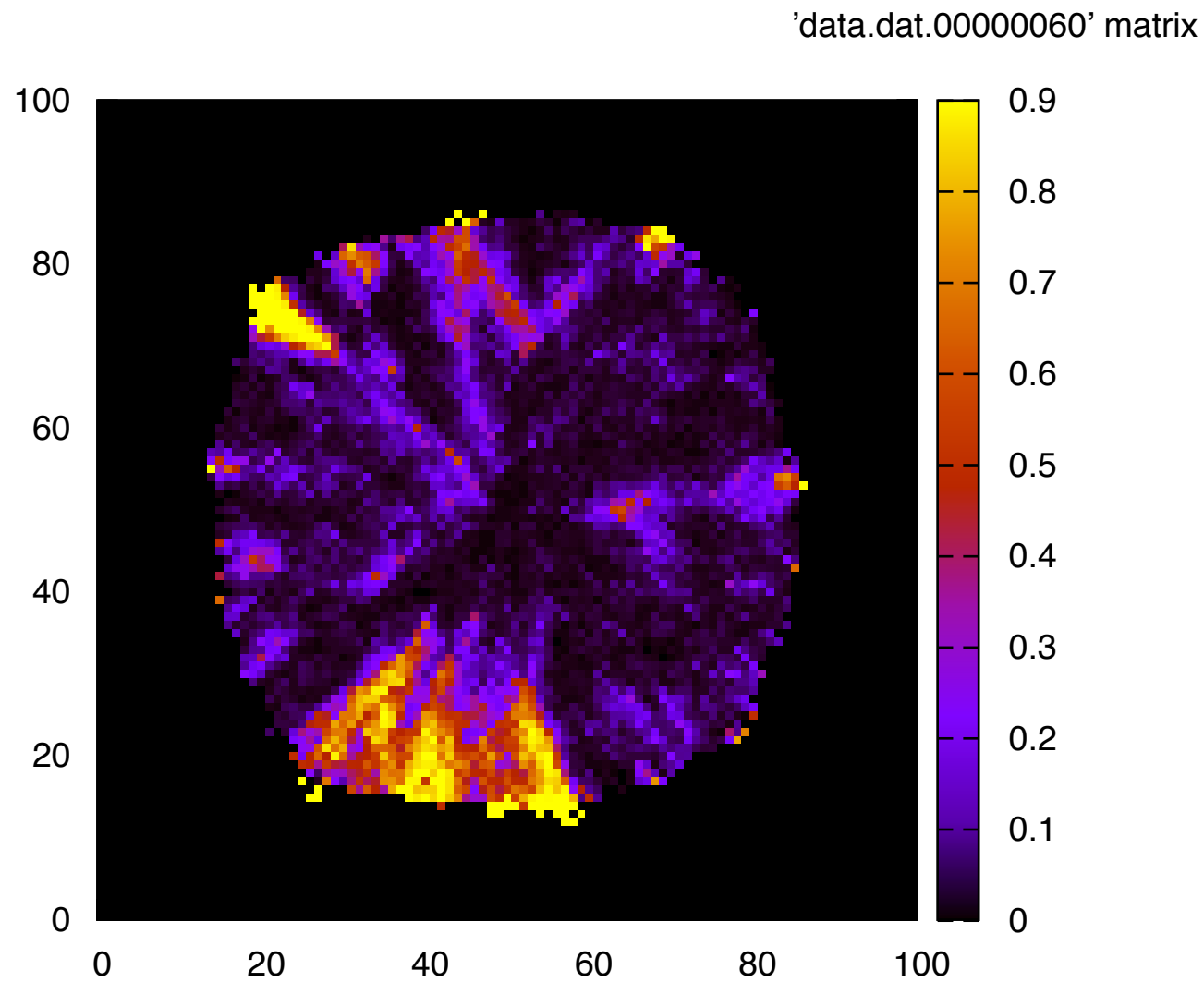
Ex3: 2D - TRACE 1 (HIGH, F=1)

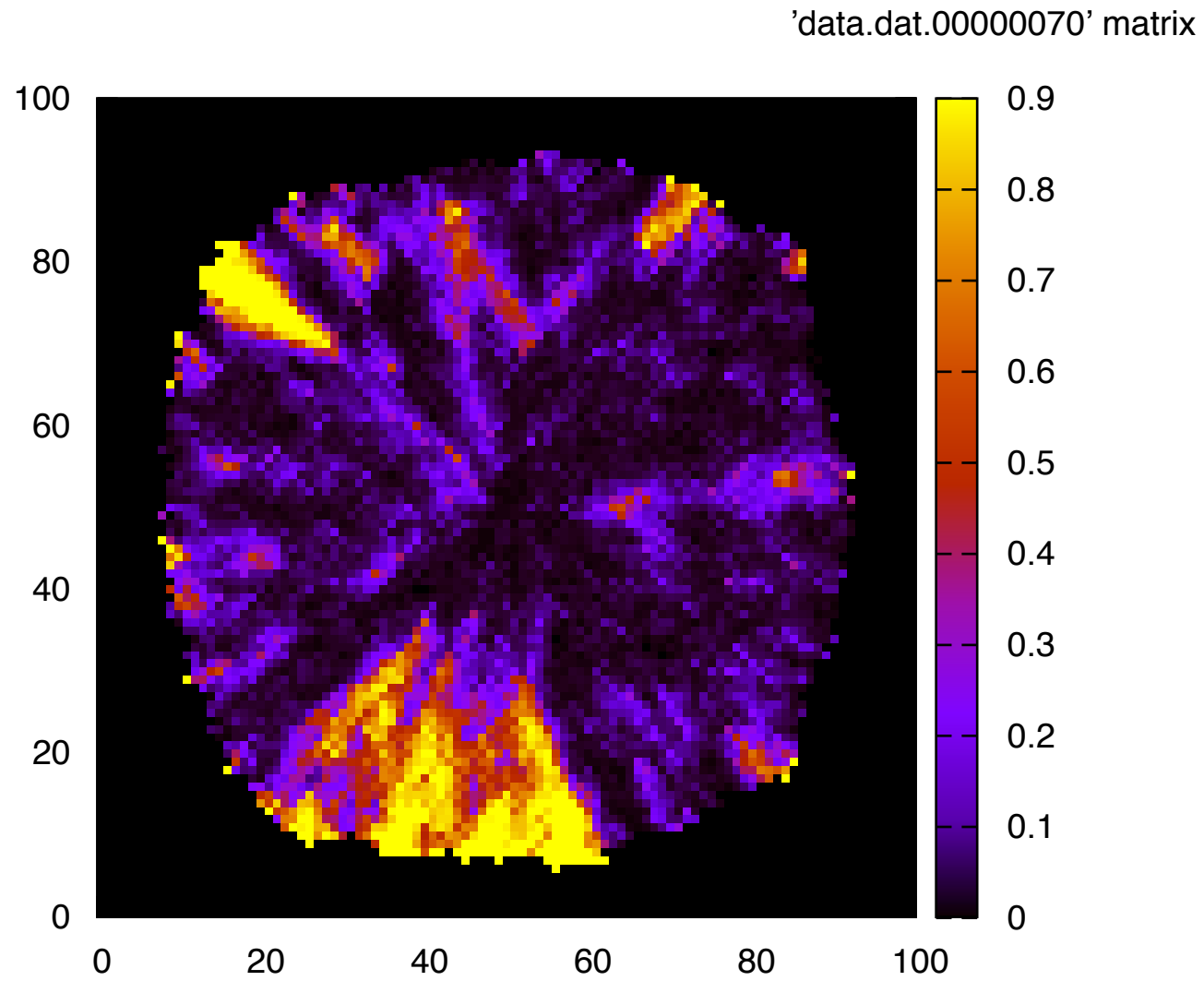


Ex3: 2D - TRACE 1 (HIGH, F=1)

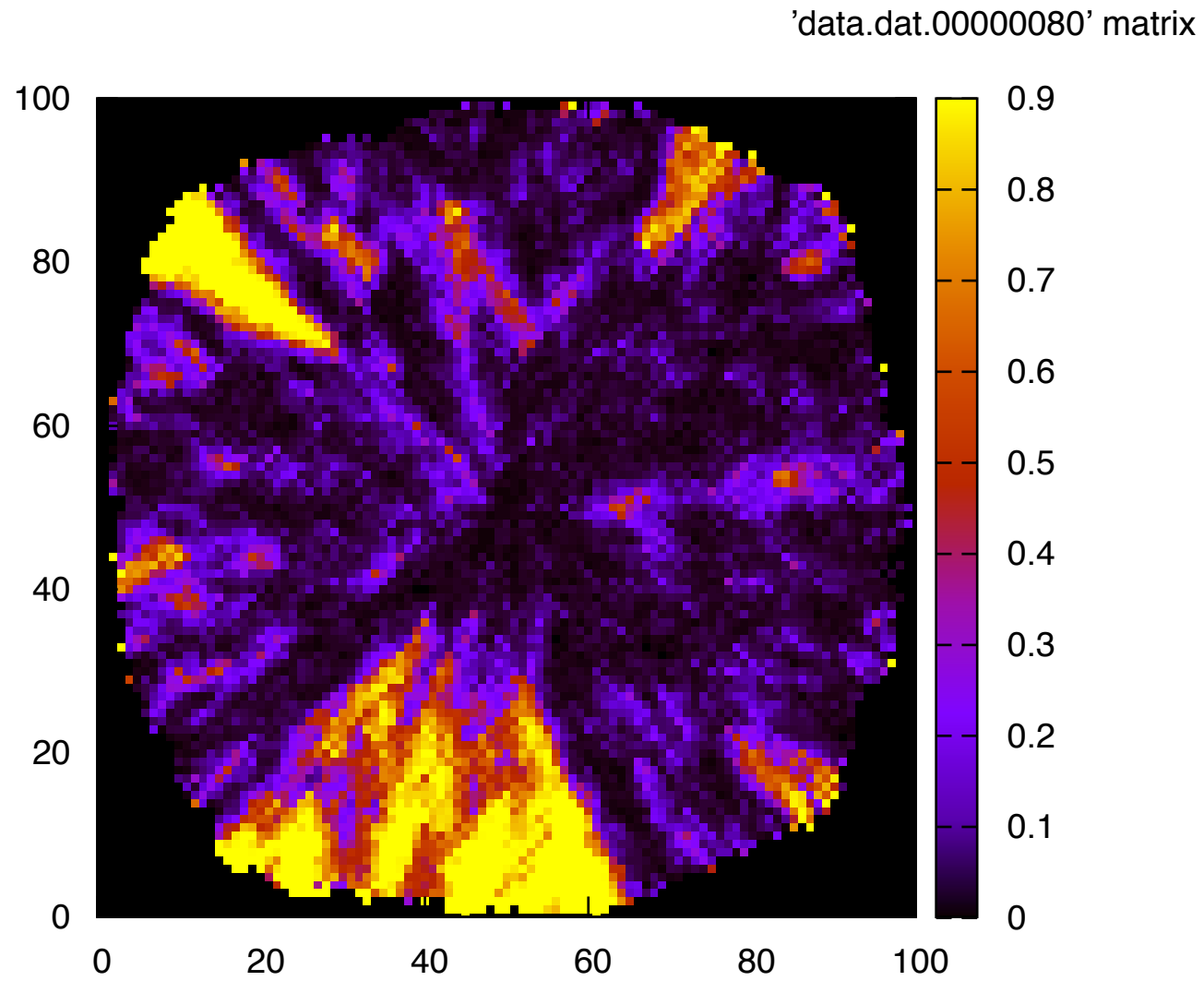


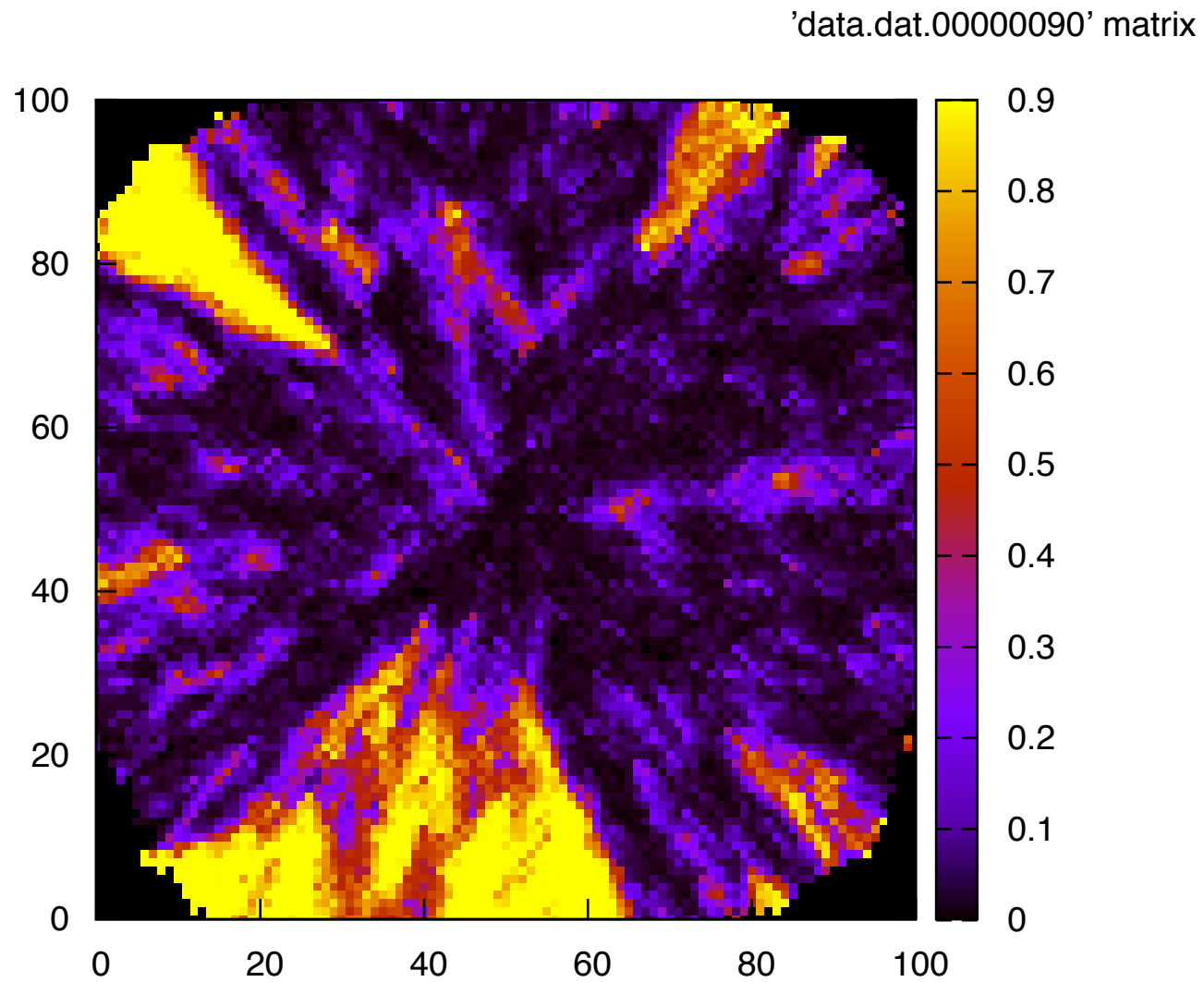
Ex3: 2D - TRACE 1 (HIGH, F=1)

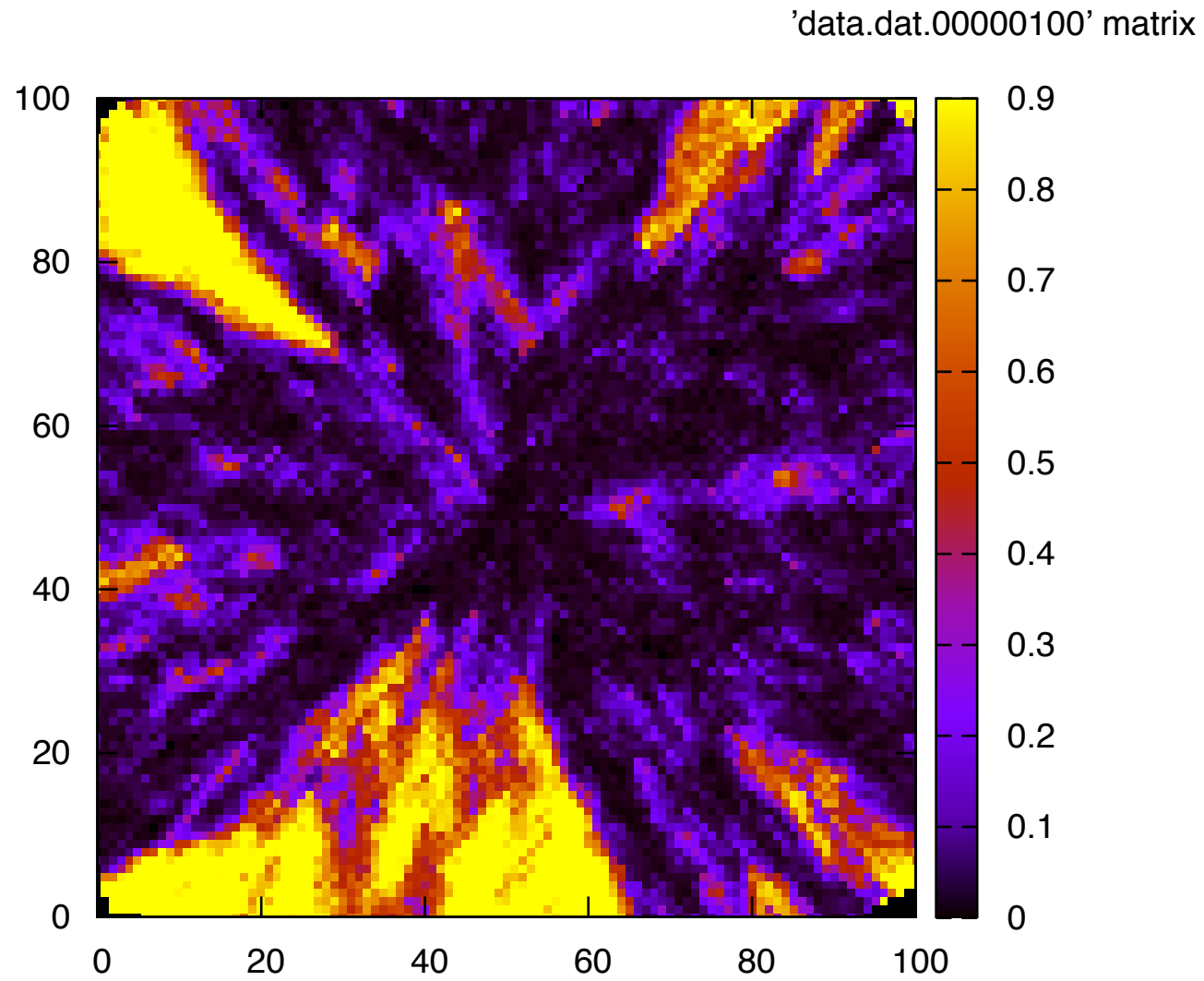


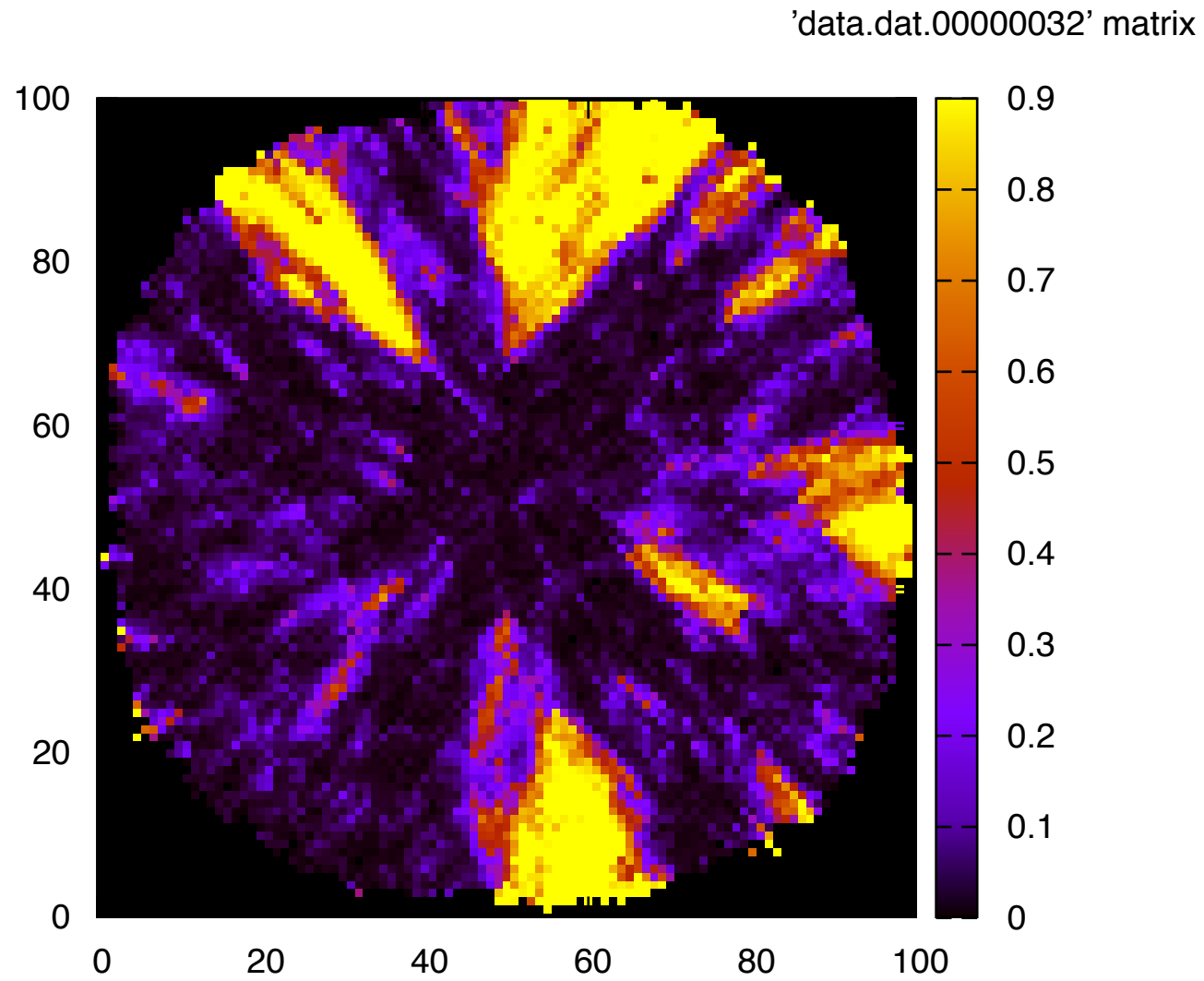


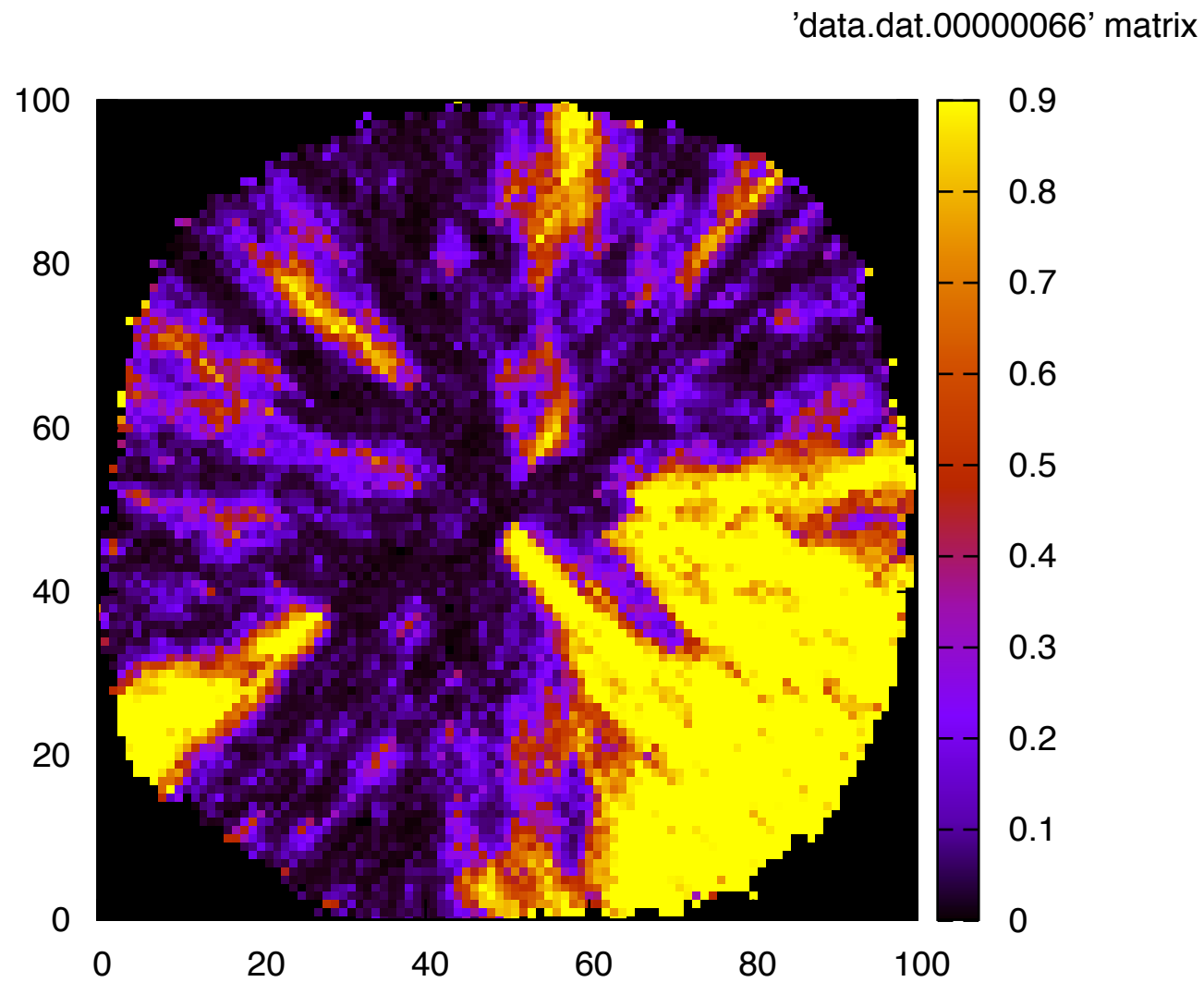
Ex3: 2D - TRACE 1 (HIGH, F=1)





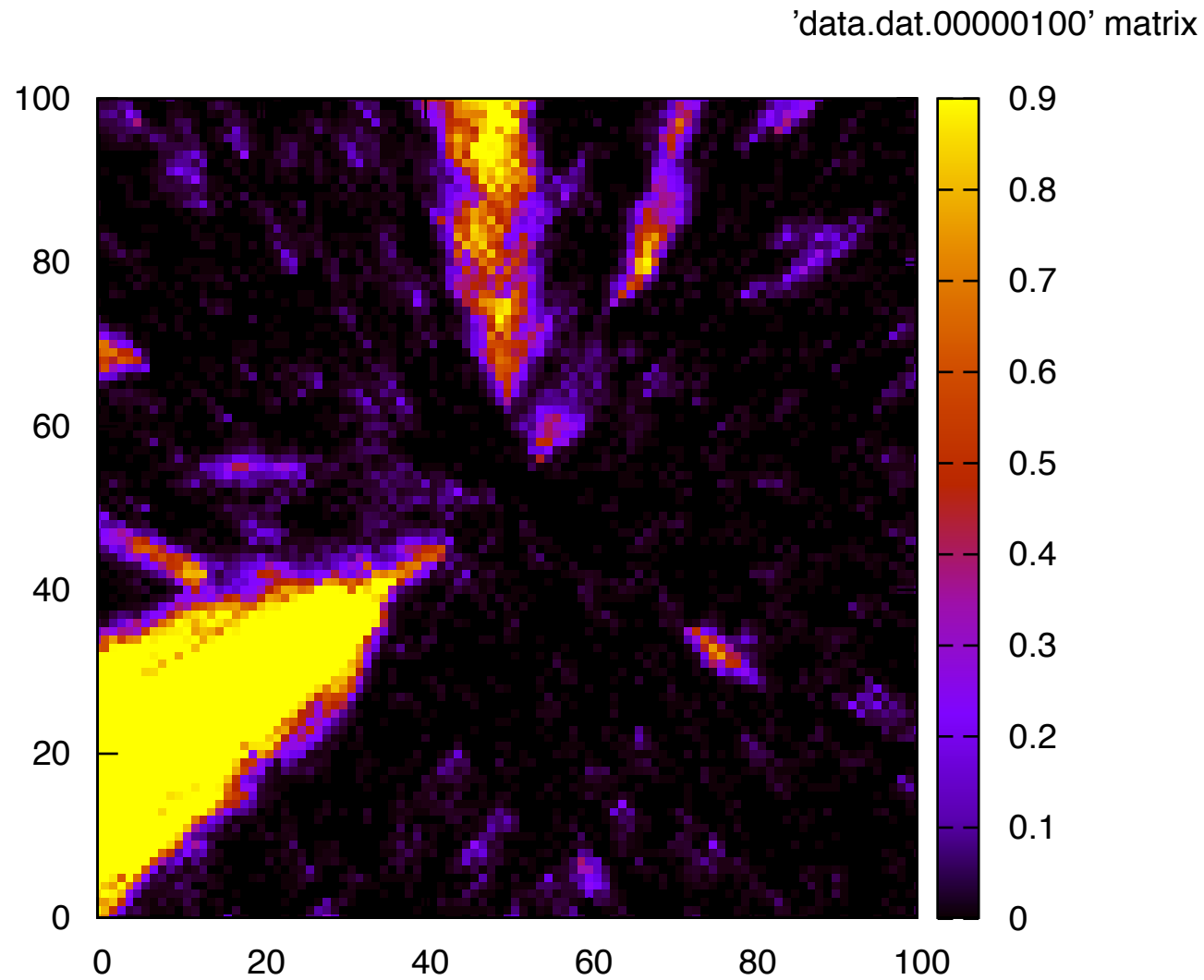






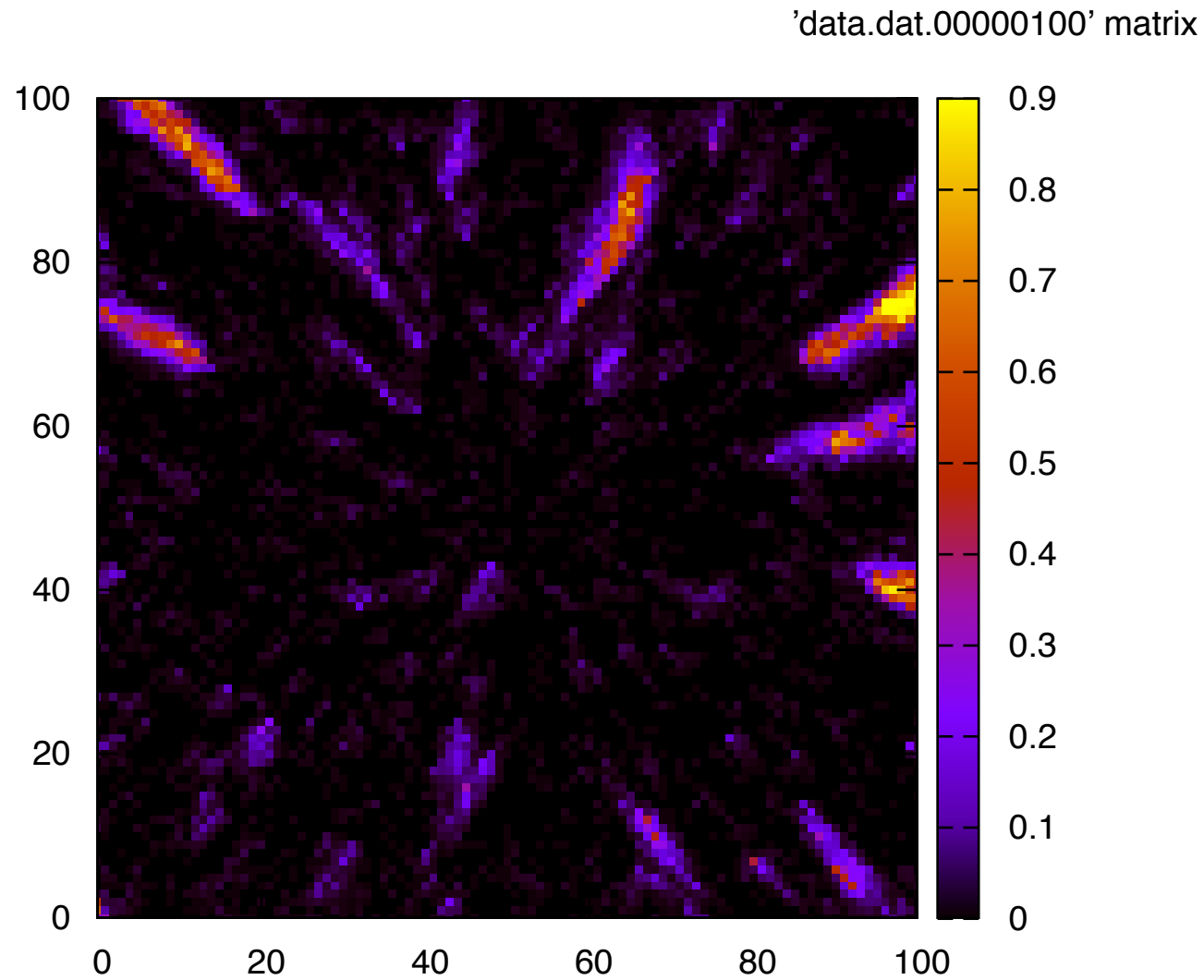
Ex3: 2D - VARYING FITNESS, TRACE 1 (MEDIUM, F=1)

PN & BioModel Engineering



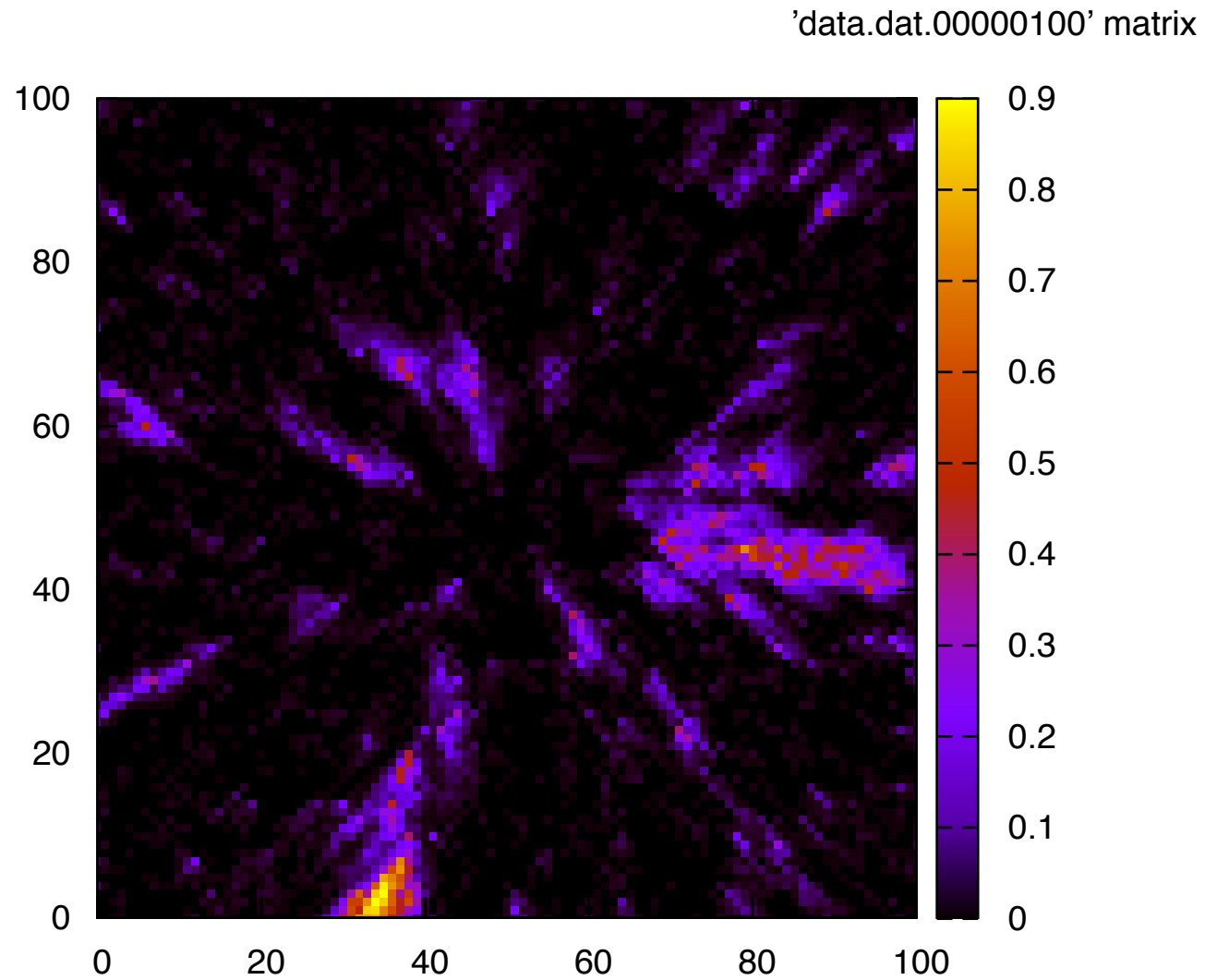
Ex3: 2D - VARYING FITNESS, TRACE 2 (MEDIUM, F=1)

PN & BioModel Engineering



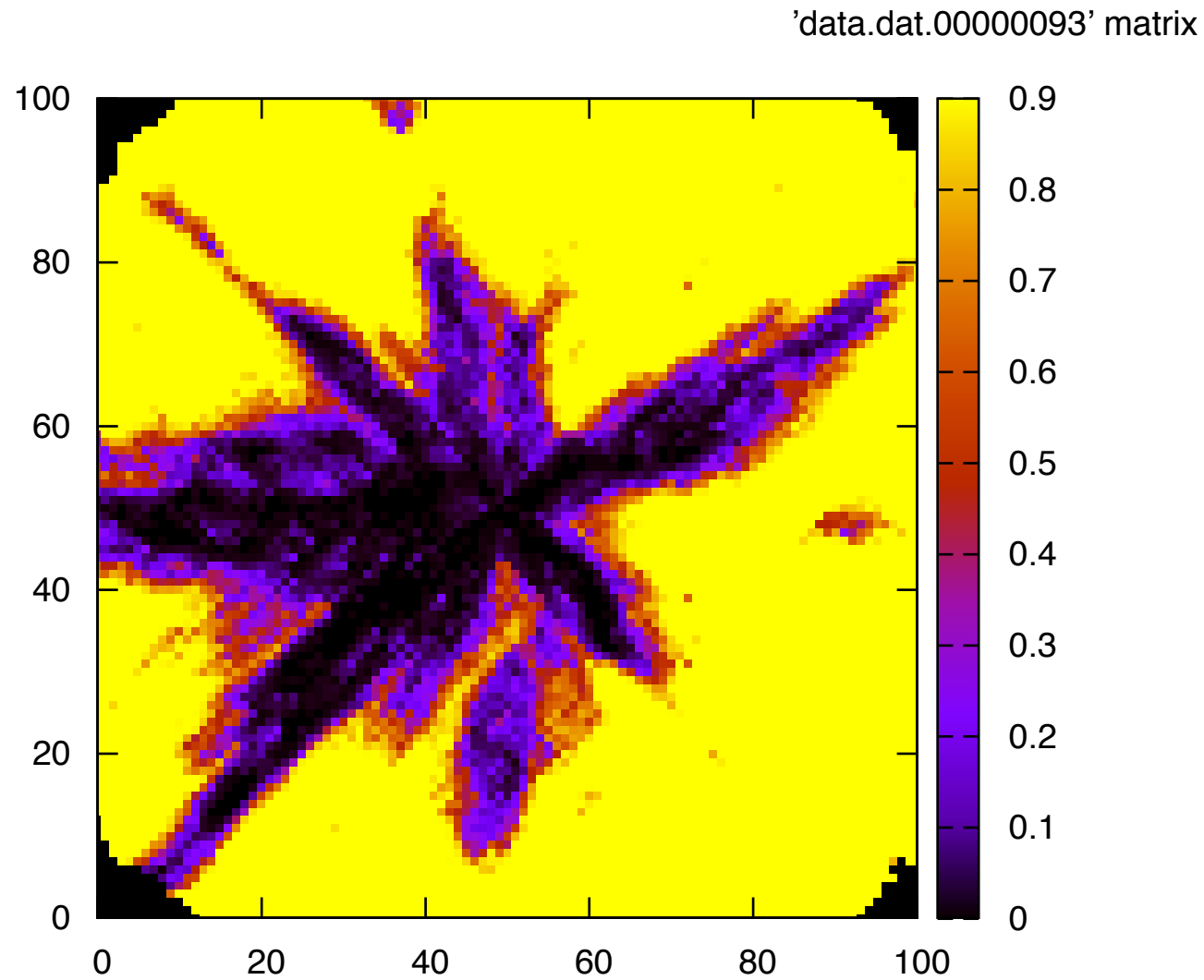
Ex3: 2D - VARYING FITNESS, TRACE 1 (MEDIUM, $F=0.99$)

PN & BioModel Engineering



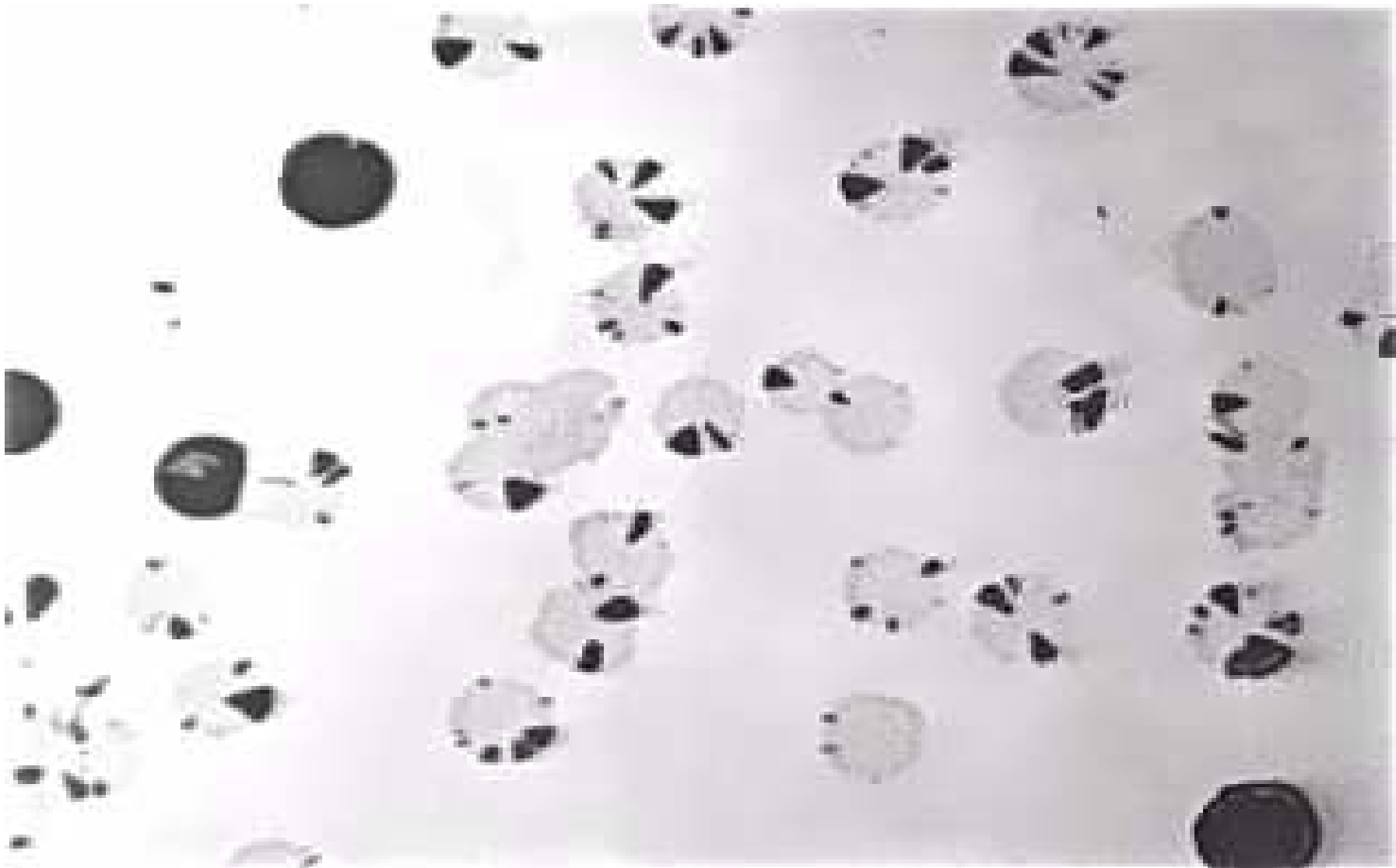
Ex3: 2D - VARYING FITNESS, TRACE 1 (MEDIUM, F=0.90)

PN & BioModel Engineering

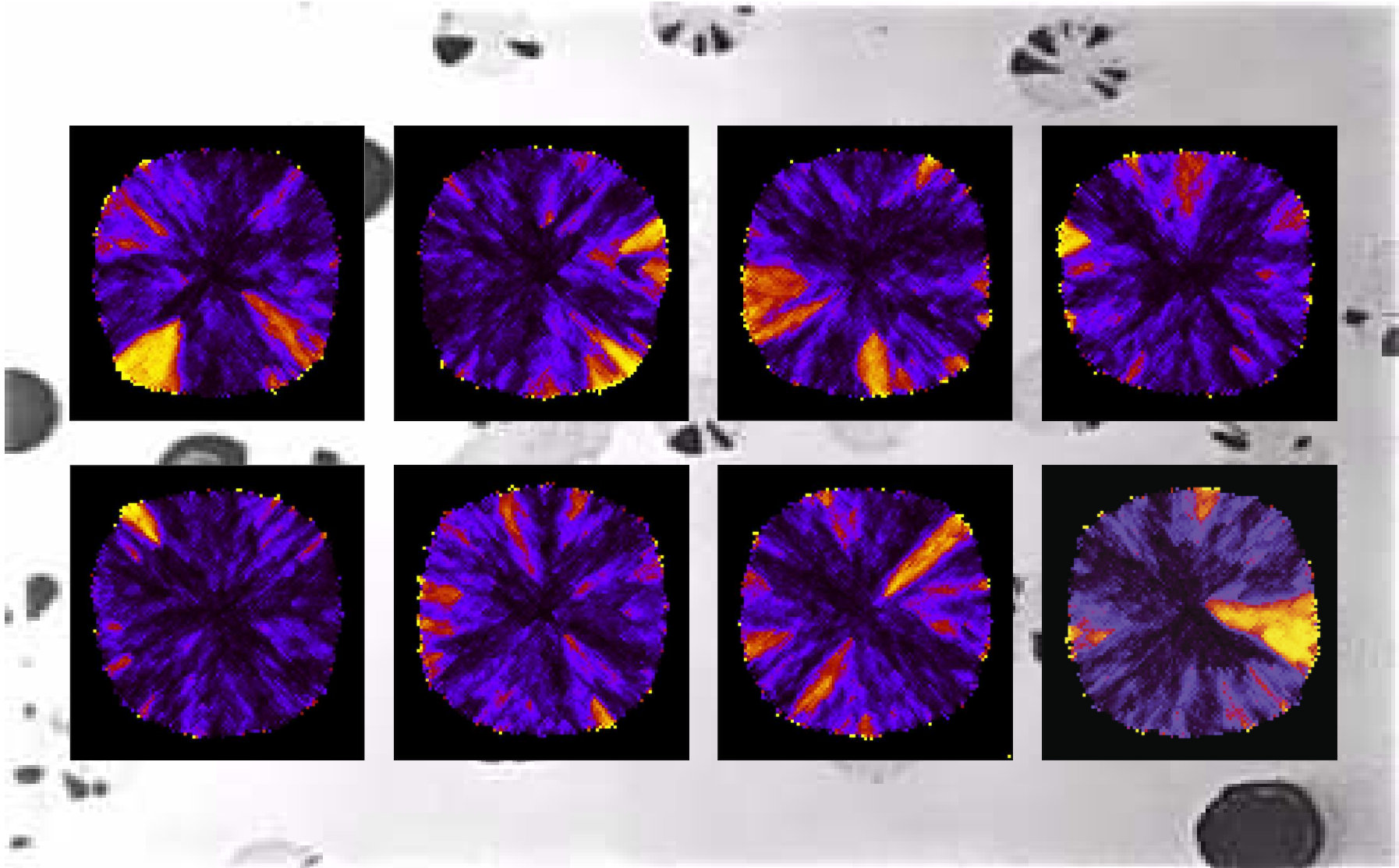


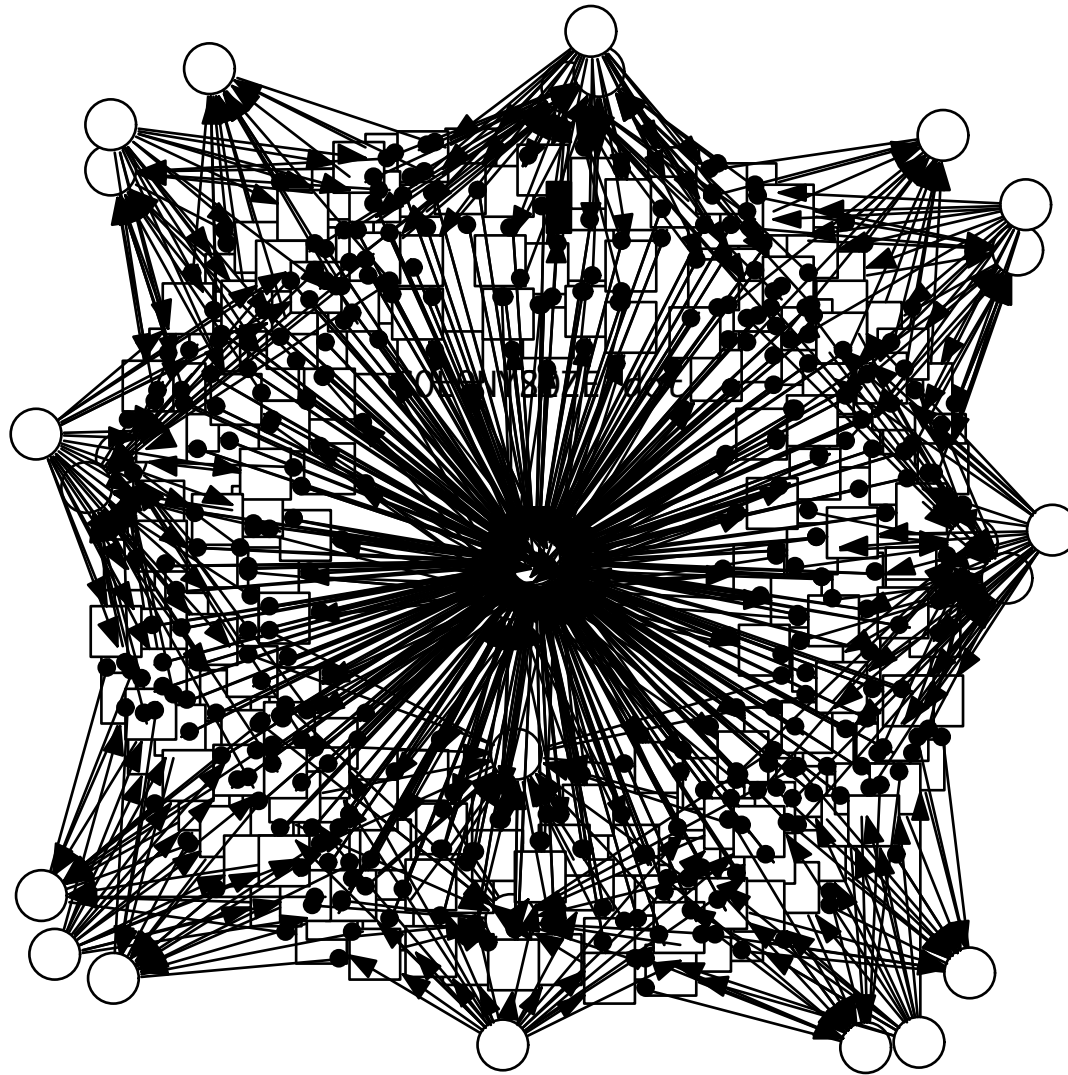
Ex3: SOME FINAL STATES (HIGH, $F=1$)

PN & BioModel Engineering



Ex3: SOME FINAL STATES (HIGH, $F=1$)



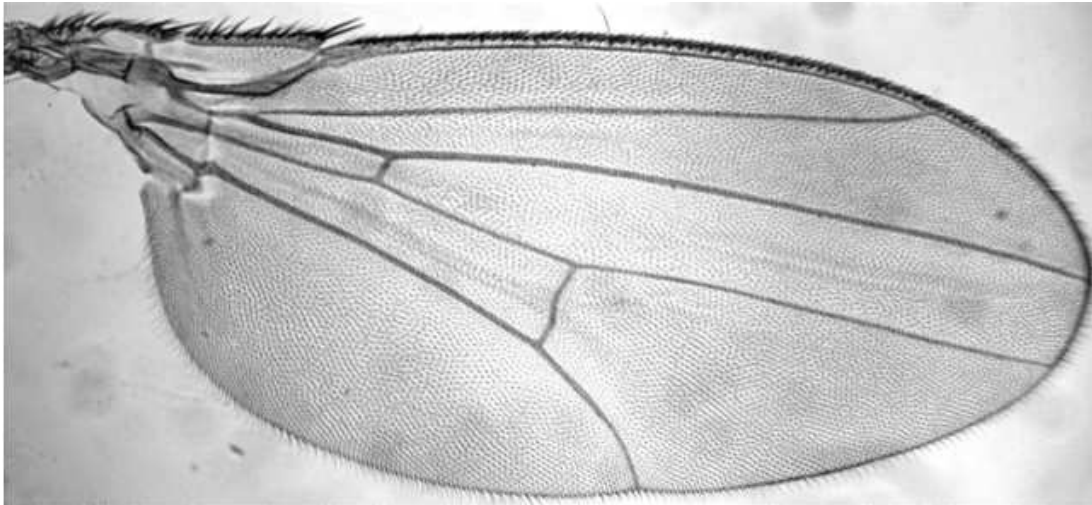


EXAMPLE 4:

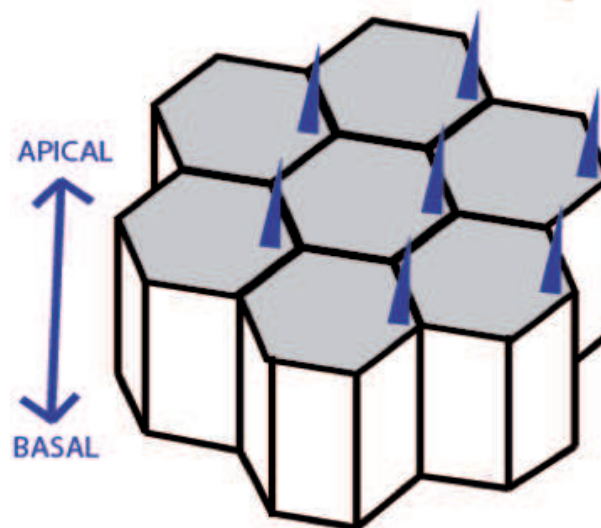
PLANAR CELL POLARITY IN FLY WING

Gao, Gilbert, Heiner, Liu, Maccagnola, Tree:
Multiscale Modelling and Analysis of Planar Cell Polarity in the Drosophila Wing;
IEEE/ACM Transactions on Computational Biology and Bioinformatics, 10(2):337-351, 2013

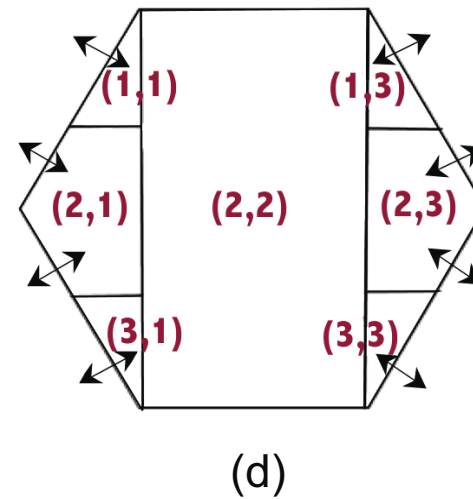
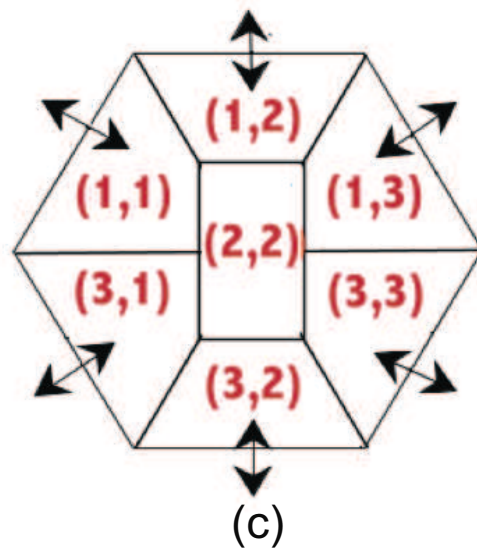
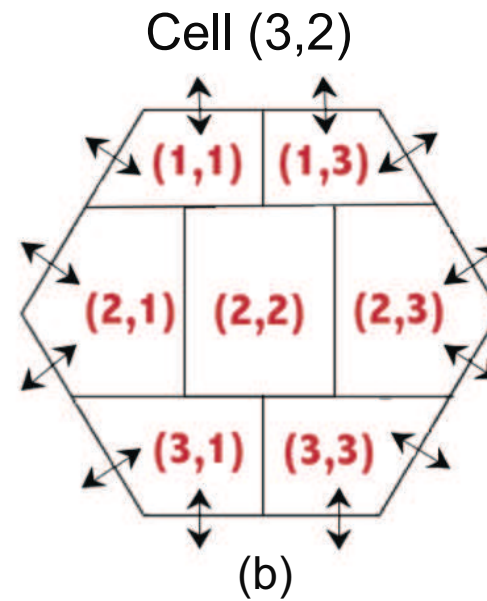
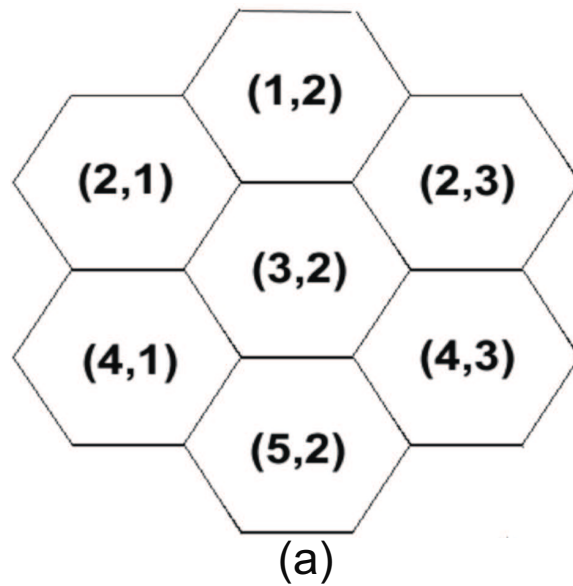
Ex4 - PLANAR CELL POLARITY

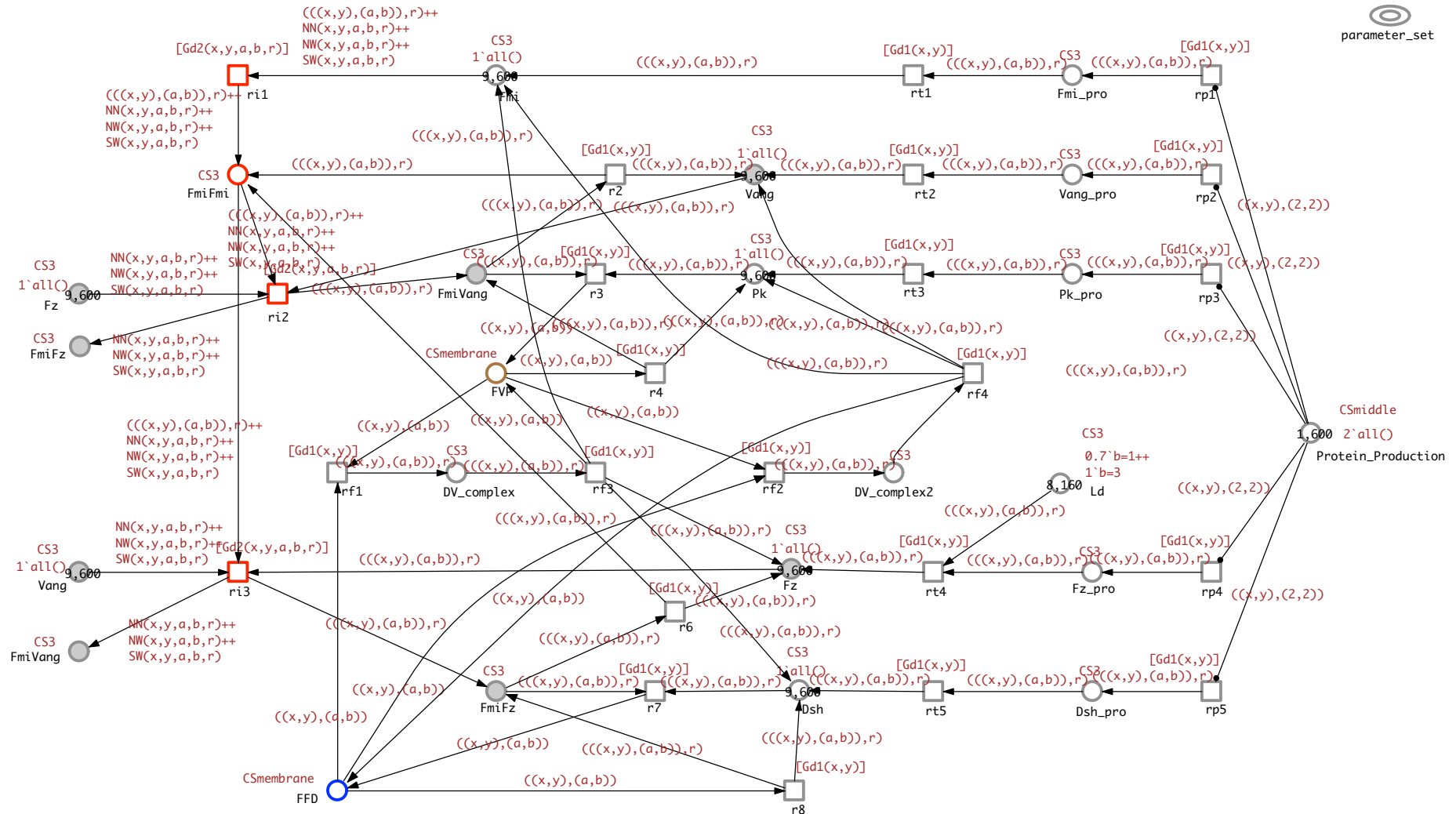


PROXIMAL $\longleftrightarrow$ DISTAL



[BioPPN 2011]
[CMSB 2011]

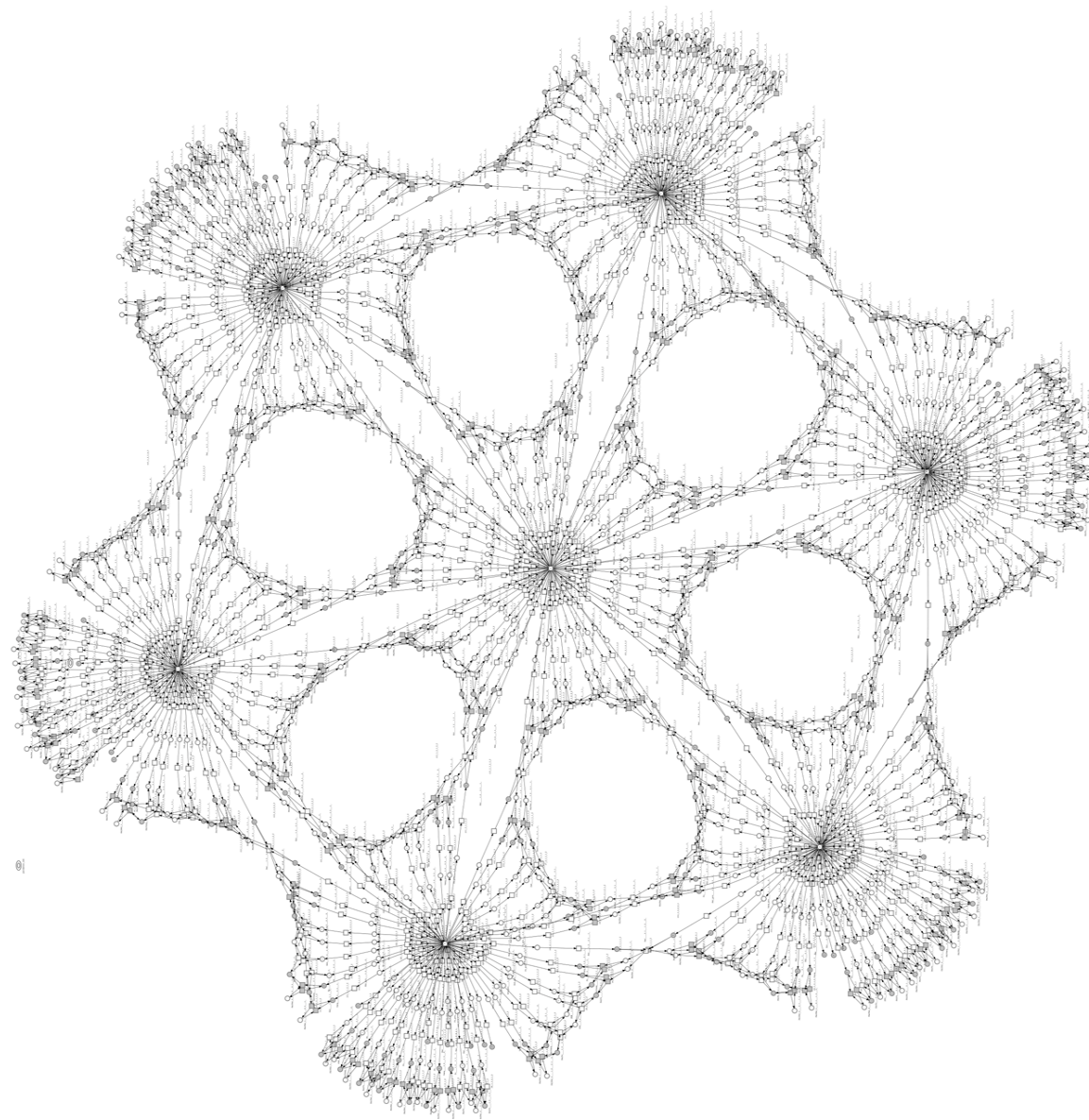




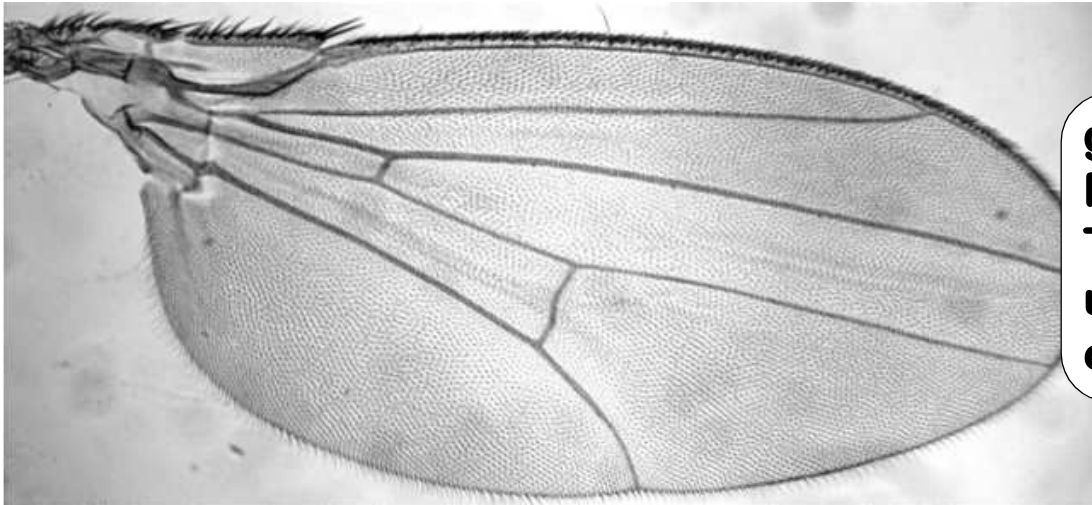
[QIAN GAO, PHD THESIS 2013]

Ex4: PLANAR CELL POLARITY, PLAIN MODEL (7 CELLS)

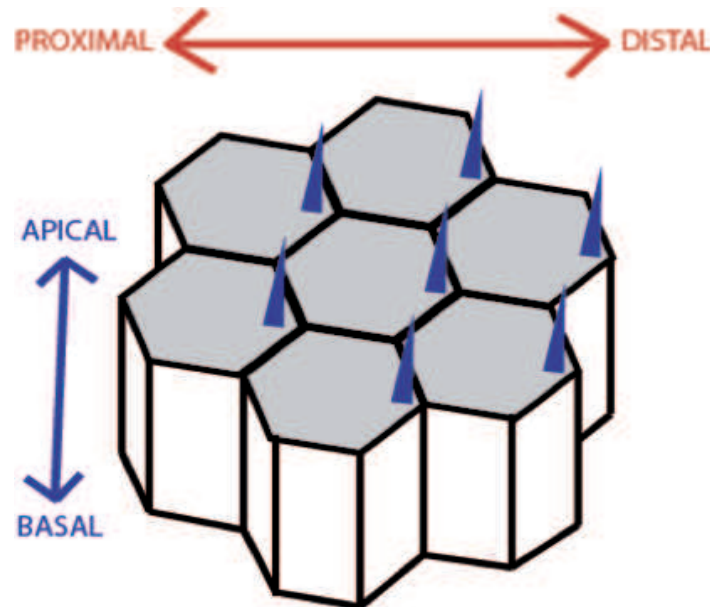
PN & BioModel Engineering



Ex4 - PLANAR CELL POLARITY



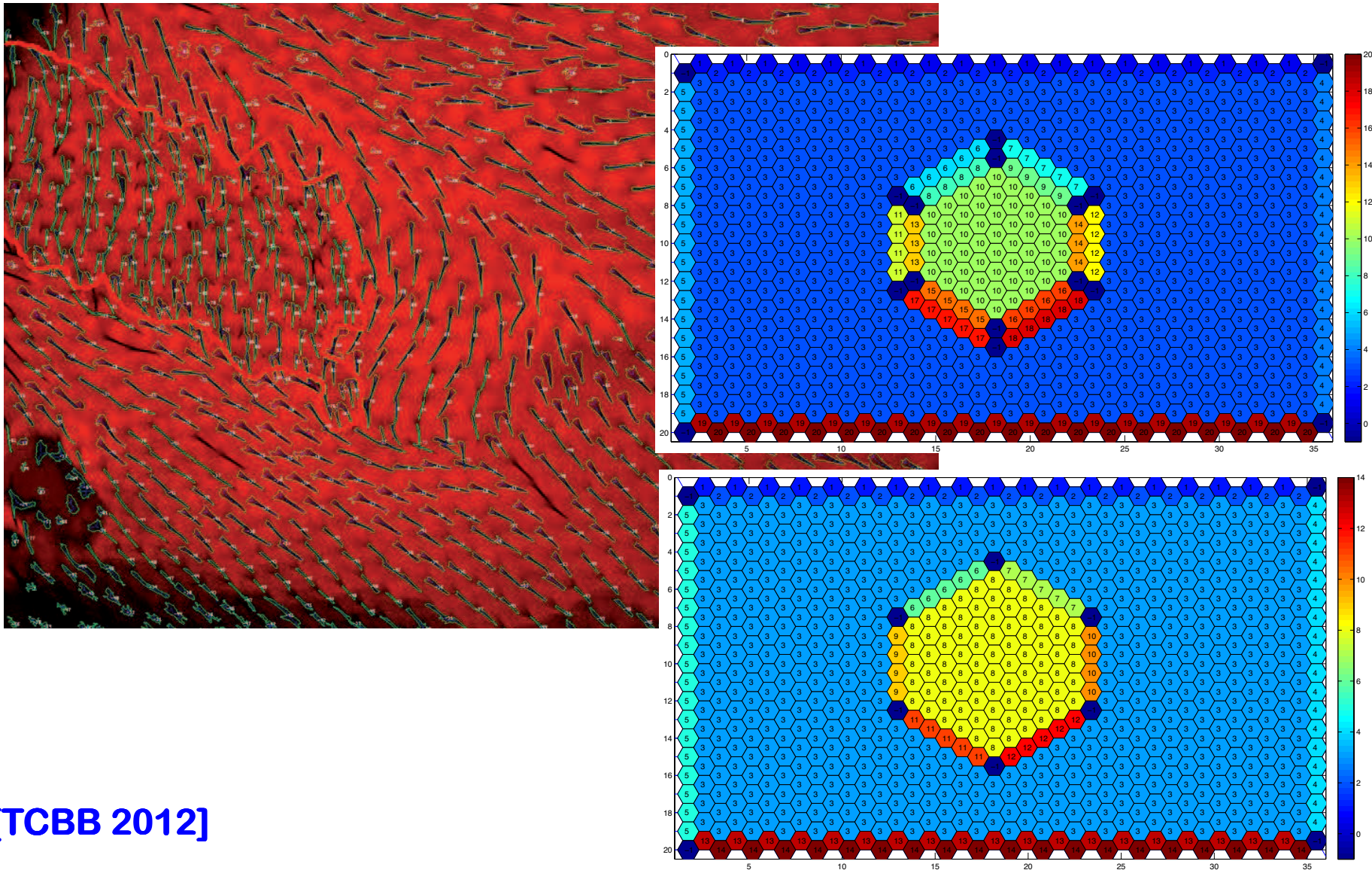
grid size:	40 x 40
PLACES:	164,000
TRANSITIONS:	229,686
unfolding:	4 min
cont. simulation:	2 h



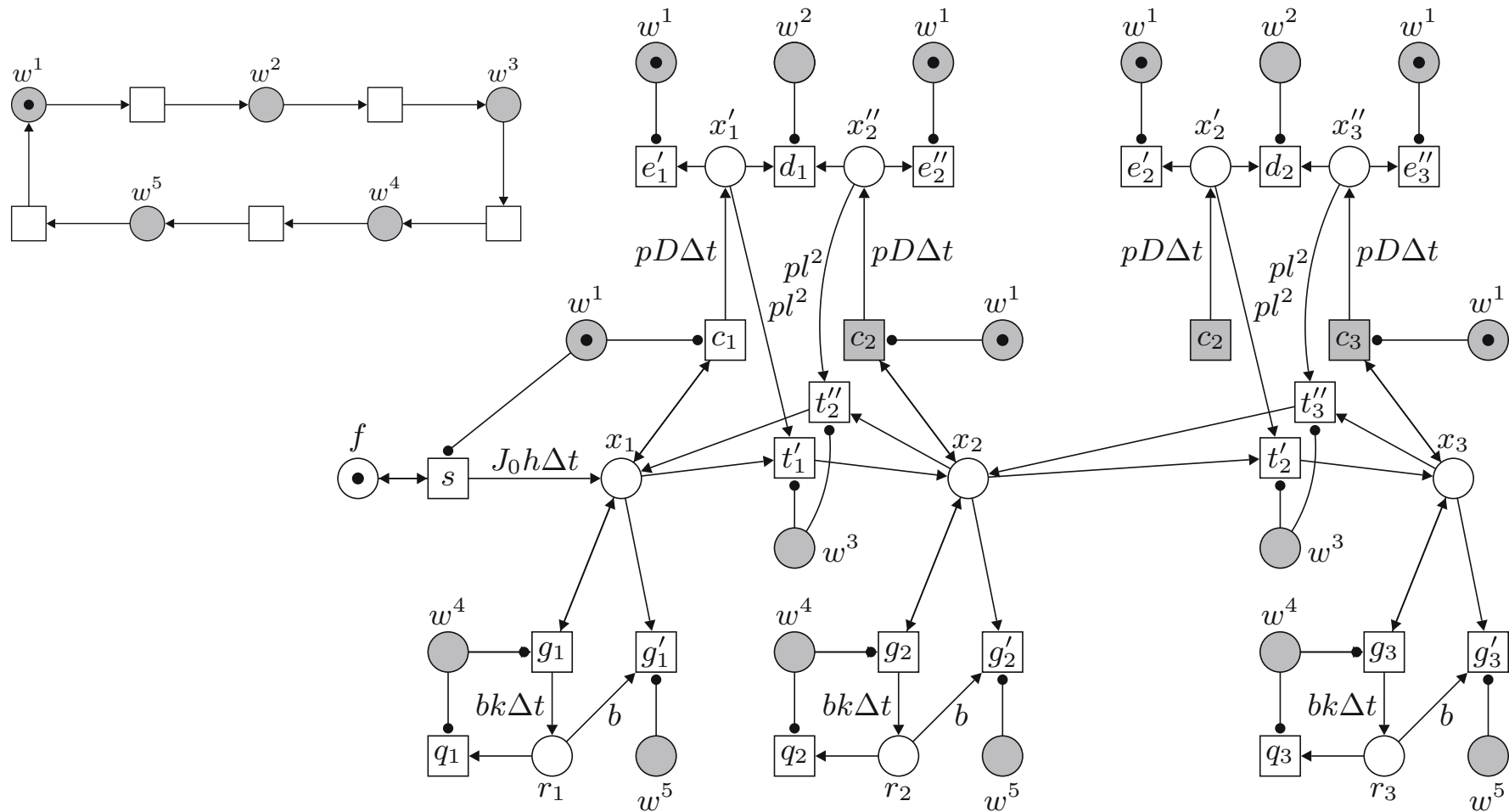
[BioPPN 2011]
[CMSB 2011]



Ex4 - PLANAR CELL POLARITY



[TCBB 2012]



Bertens, Kleijn, Hille, Heiner, Koutny, Verbeek:
 Modeling biological gradient formation: combining partial differential equations and Petri nets;
 Natural Computing 2015.

❑ FRAMEWORK

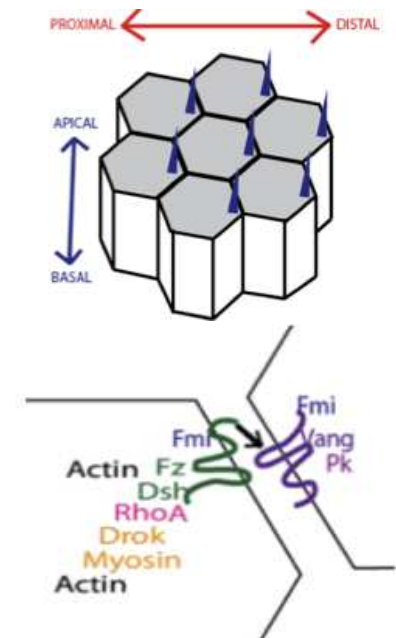
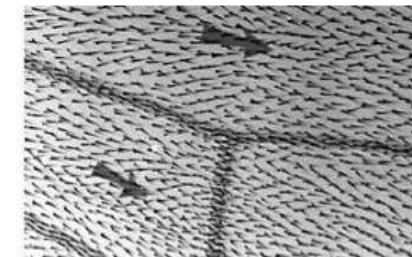
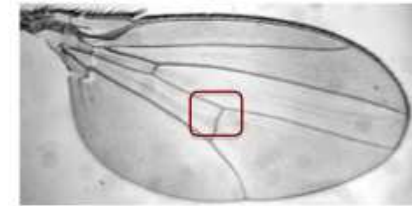
- > QPN - SPN - CPN - HPN
- > uncoloured / coloured

❑ MODELLING BIO PETRI NETS

❑ COLOUR

- > gradients
- > phase variation
- > fly wing

❑ WHAT NEXT ?



❑ FRAMEWORK

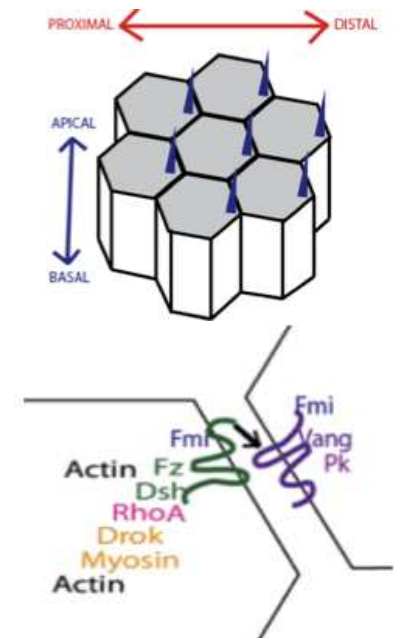
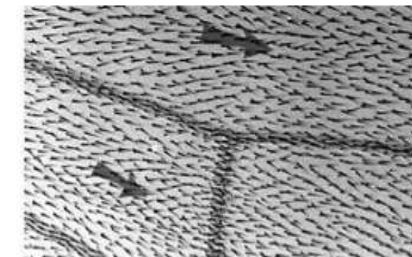
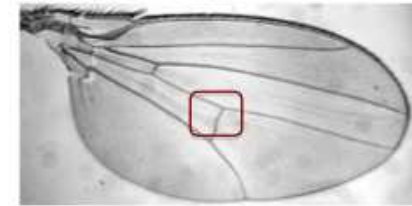
- > QPN - SPN - CPN - HPN
- > uncoloured / coloured

❑ MODELLING BIO PETRI NETS

❑ COLOUR

- > gradients
- > phase variation
- > fly wing

❑ WHAT NEXT ? -> MODELLING 4 ANALYSING



❑ FRAMEWORK

- > QPN - SPN - CPN - HPN
- > uncoloured / coloured

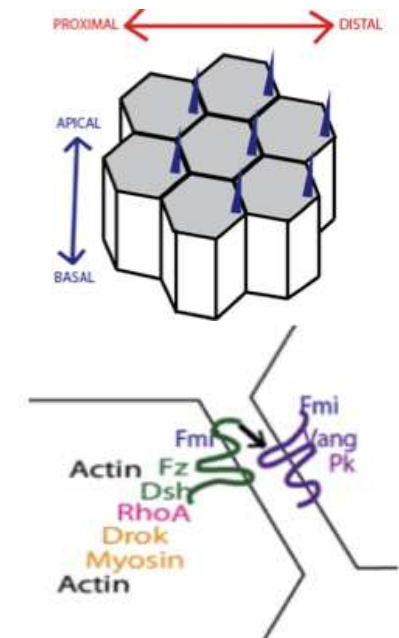
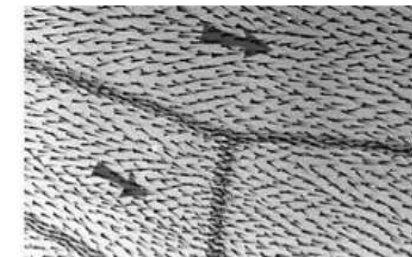
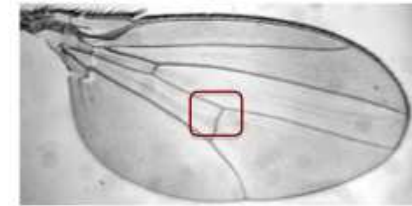
❑ MODELLING BIO PETRI NETS

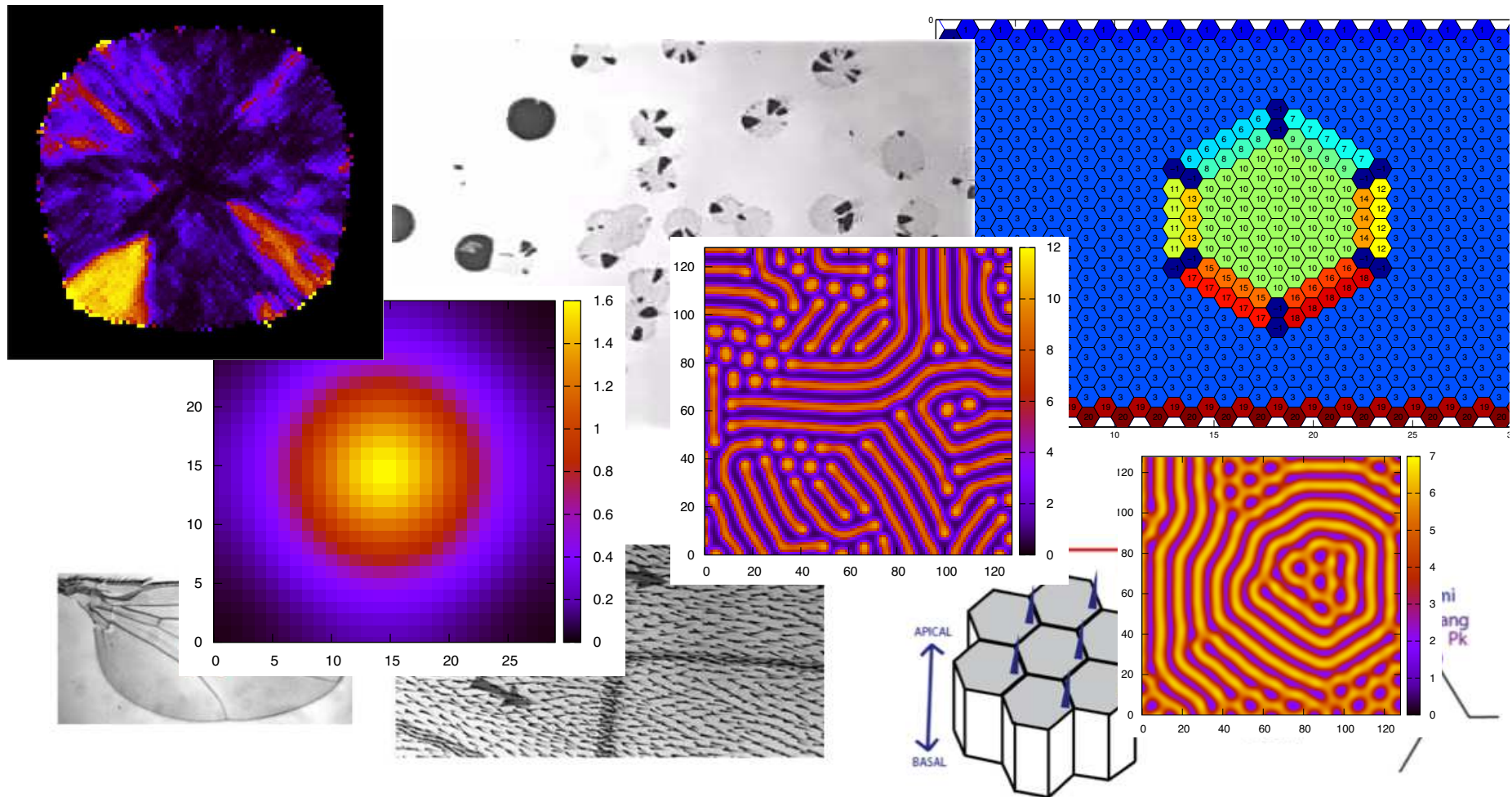
❑ COLOUR

- > gradients
- > phase variation
- > fly wing

❑ WHAT NEXT ? -> MODELLING 4 ANALYSING

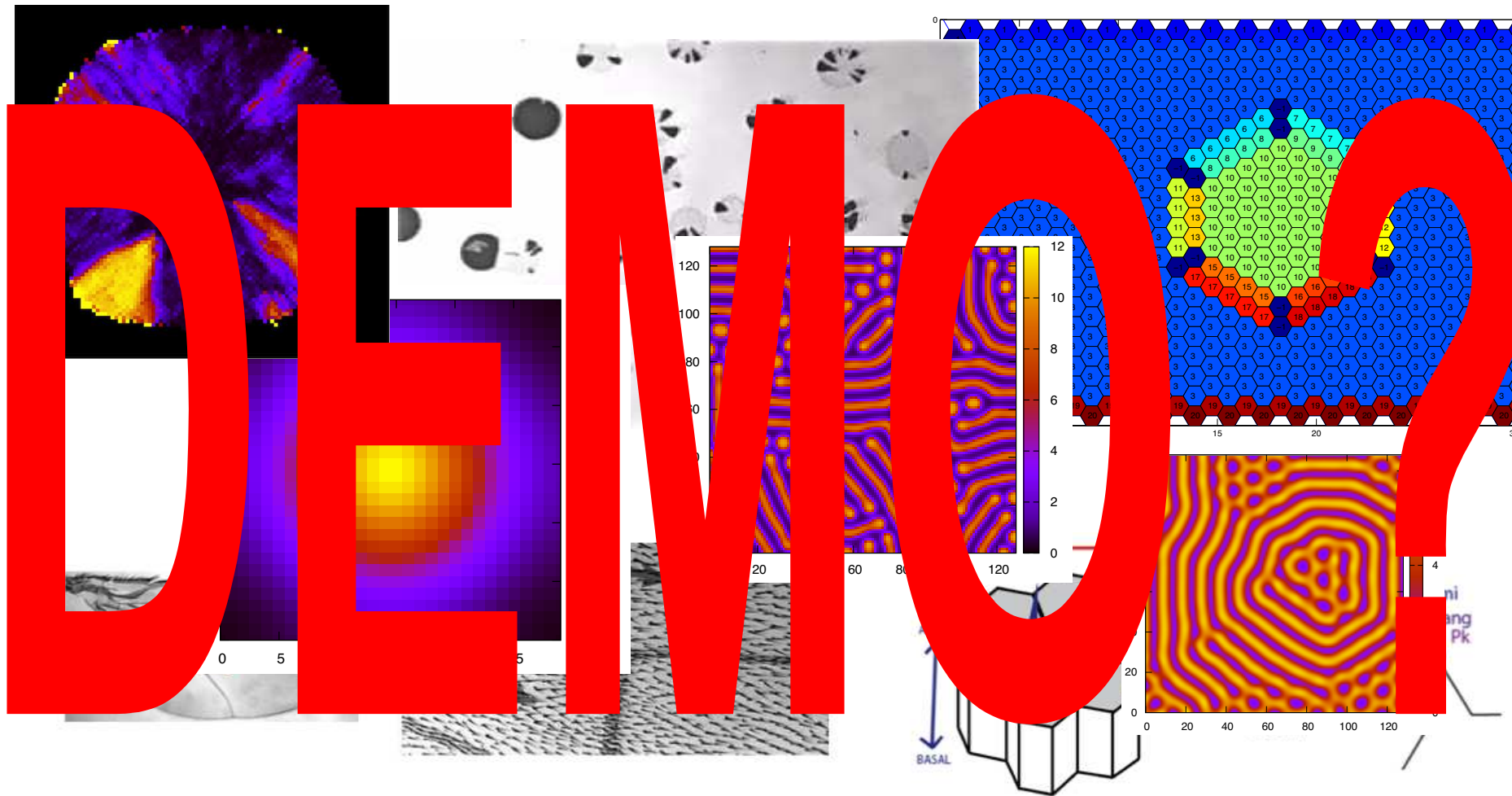
- > how to analyse coloured Petri nets ?
- > model checking
- > efficient hybrid simulation





[HTTP://WWW-DSSZ.INFORMATIK.TU-COTTBUS.DE](http://www-dssz.informatik.tu-cottbus.de)

[HTTP://MULTISCALEPN.BRUNEL.AC.UK](http://multiscalepn.brunel.ac.uk)



[HTTP://WWW-DSSZ.INFORMATIK.TU-COTTBUS.DE](http://www-dssz.informatik.tu-cottbus.de)

[HTTP://MULTISCALEPN.BRUNEL.AC.UK](http://multiscalepn.brunel.ac.uk)